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Principles and Practice of Interventional Pulmonology

Springer

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Armin Ernst • Felix J.F. Herth
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Preface

The inception for this book dates back several years after both of us heard numerous times from participants in our courses the request for a comprehensive text covering all aspects of Interventional Pulmonology (IP) and providing both a pathophysiologic background as well as illustrated and clear instructions on how procedures ought to be performed. A review at that time confirmed that shorter texts and review articles were available, but a comprehensive textbook for the whole field was indeed missing.

As with any growing specialty in medicine, the amount of information and knowledge continues to grow. A few years ago, IP would have been thought of as mainly being applicable to patients with malignant airway obstruction – now the interventional pulmonologist is a central member of the team in the staging and management of lung cancer, management of obstructive airway diseases, pleural disorders and other lung diseases. The many chapters in this book reflect this trend and reality. The depth of the material reflects how Interventional Pulmonology is not just about how to do something but also when and why (or why not) to intervene.

This work would not have been possible without the gracious support from the many authors representing multiple subspecialties, highlighting the multidisciplinary nature of the field. We are clearly indebted for their willingness to share their knowledge and contribute to the education of the ones eager to learn. Also, this book would not have been possible without the help of our editors Kevin Wright and Portia Levasseur from Springer. Sarah Rego kept everybody on track and ensured that we all stayed in the allotted time frame and our thanks to her as well.

We hope you enjoy the book and that it proves a helpful companion in your medical practice.

Boston, MA, USA — Armin Ernst
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Part I

General Topics

History of the Rigid Bronchoscope

1

Heinrich D. Becker

Introduction

O. Kollofrath, assistant to Gustav Killian at the Poliklinik of Freiburg University, Germany, wrote in his article titled: "Entfernung eines Knochenstücks aus dem rechten Bronchus auf natürlichem Wege und unter Anwendung der directen Laryngoskopie" (Münchener Medicinische Wochenschrift No. 38, September 1897), "On March 30th of this year I had the honor to assist my admired principal, Herrn Prof. Killian in extraction of a piece of bone from the right bronchus. This case is of such peculiarity with respect to its diagnostic and therapeutic importance that a more extensive description seems justified." In order to understand this statement one has to consider the state of the art of airway endoscopy at his time.

The Pre-endoscopic Era

Access to the airways in the living patient was tried by Hippocrates (460–370 BC), who advised the introduction of a pipe into the larynx in a suffocating patient. Avicenna of Buchara (about 1000 AD) used a silver pipe for the same purpose. Around 1542, Vesalius observed that the heartbeat and pulsation of the great vessels stopped when he opened the chest of an experimental animal, but it returned, again, after he introduced a reed into the airway and inflated the lungs by the use of bellows. This made him assume that the trachea was part of the circulating system. This is why he called it "the rough artery" ("τραχυσ" in Greek language or arteria aspera in Latin).

Desault (1744–1795) advised nasotracheal intubation for the treatment of suffocation and removal of foreign bodies. Still in his time, inhalation of a foreign body in over half of cases resulted in death or chronic illness due to purulent infection, abscess, fistulas, and malnutrition. Several instruments had been designed for blind removal from the airways via the larynx or a tracheotomy (called "bronchotomy"), which was also used for the treatment of subglottic stenosis in diphtheria. But until far into the second half of the nineteenth century tracheotomy had a high mortality of up to more than 50%. This is why methods were developed for blind intubation. But when Horace Green in 1846 presented his "Treatise on the Diseases of the Air Passages" to the Commission of the New York Academy of Medical Sciences, he was blamed for presenting "…a monstrous assumption, ludicrously absurd, and physically impossible,…an anatomical impossibility and unwarrantable innovation in practical medicine" and was removed from the society. It was Joseph O'Dwyer who persisted and introduced the method for emergency intubation of diphtheric children.

The Development of Endoscopy

Instruments for the inspection of body cavities such as mouth, nose, ear, vagina, rectum, urethra, and others had been in use for ages, and descriptions are found in Egyptian papyri, Greek, and Roman texts. Yet, Porter in 1838 still stated: "There is perhaps no kind of disease covered by greater darkness or posing more difficulties to the practitioner than those of the larynx and the trachea," because till then the larynx could be only insufficiently inspected by forceful depression of the tongue with a spatula, a so-called glossokatochon. Nobody had ever looked into the living trachea. It was only after three major inventions, direct inspection of the airways and visually controlled treatment became possible: (1) Dedicated instruments for inspection, (2) suitable light sources, and (3) efficient anesthesia.

The Laryngeal Mirror

Experiments for the inspection of the larynx by mirrors had been performed among others by Latour (1825), Senn (1829),

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Belloc (1837) Liston (1840), and Avery (1844). However, it was not a physician but a singing teacher in London, Manuel Garcia, who first observed his own larynx in 1854 with the help of a dental mirror that he had seen at the world exhibition in Paris and bought from the French instrument maker Charriére. Almost at the same time, without knowing his work, in 1856 the laryngologist Ludwig Türck in Vienna performed first experiments with a similar device. In winter when the illumination by daylight was no longer sufficient for continuation of his studies, he lent the device to the physiologist Czermak in Budapest, then part of the Austro-Hungarian Empire. Czermak published results in laryngeal inspection before Türck, which resulted in a long fight over rights of priority, the so-called Türkenkrieg (Turks war).

By the application of the laryngeal mirror, diagnosis and treatment of laryngeal diseases became much easier, so that G.D. Gibb in 1862 said: "It has fallen to my lot to see cases of laryngeal disease…that have existed for 10 or 20 years, and submitted to every variety of treatment, without the slightest benefit, at the hands of some of the foremost amongst us, wherein the symptoms have depended upon a little growth attached to one or both vocal chords, which was recognized in as many seconds as the complaints had existed years. The nature of the malady thus being made out, the plan of treatment to be persued became obvious." And it was also in 1862 that the German surgeon Victor von Bruns in Tübingen, with the help of this laryngoscopic mirror, could remove the first polyp from the vocal chord in his own brother. Without suitable anesthetics, the procedure needed weeks of preparation by stepwise suppression of the gagging and coughing reflexes on the patient's side, who had to repeatedly introduce a probe into the pharynx, while the physician rehearsed the procedure with a little knife by training on a severed head from a corpse that was hung on the wall. Later he rehearsed with blunt instruments on larynxes of volunteers. Also his report was rejected as "…a daring deed that should not be imitated and the practical importance of which seems less as there would be hardly another opportunity for its repetition." One of the major problems was the indirect and reverse view of the image, which added to the difficulties.

The First Endoscopes and Light Sources

In contrast to other fields of endoscopy, where daylight or candlelight could be introduced for inspection of the vagina, rectum, urethra, etc., it was only after Philipp Bozzini, general practitioner at Frankfurt, had developed his "illuminator" in 1805 that a suitable light source became available. The device consisted of a box with a candle inside, the light of which was reflected by a hollow mirror into a "conductor," a split metallic tube that could be spread by a simple mechanism. For the inspection of organs that could not be visualized by direct inspection, he used a tube with a mirror inside the tip of the tube, for reflection of the light and image.

The first really suitable successor after Bozzini's illuminator was the instrument of Desormeaux, who in 1853 also introduced the word "endoscope" for his instrument to inspect the body cavities. By applying Desormeaux's endoscope, A. Kußmaul in 1867/1868 performed the first inspection of the esophagus. The illumination by spirit, however, was insufficient for the inspection of the stomach. The first suitable gastroscope, constructed by Leiter in Vienna, was used in 1881 by von Mikulicz. It was a closed optic with lenses and prisms. Illumination was provided by an electric glowing platinum wire at the tip of the instrument which had to be cooled by a constant flow of water and thus was not suitable for application in the airways, because of its dimensions.

Esophagoscopy was performed mainly by the use of hollow tubes and spatulas that were connected to proximal illumination sources. It was also the Viennese Endoscope maker Leiter who in 1886 produced the first so-called panelectroscope, a tube that was connected to a handle that contained an electric bulb and a prism for illumination. The instrument was modified by many specialists, such as Gottstein, who was the first to attach a metal tube in 1891, by Rosenheim, who accidentally first passed into the trachea. Kirstein in Berlin intentionally started to intubate the larynx with the esophagoscope, and after his first experience in 1894 began systematic direct inspection, which he called "autoscopy" (Greek: "αυτοσ", by himself, meaning directly without help of a mirror). "…I convinced myself… that one can pass the vocal chords intentionally with a middle sized esophagoscope into the cocainized trachea and right down to the bifurcation; this experience should be eventually fructified." But "The region of the lower trachea is a very dangerous place!… The rhythmic protrusion of its wall is…a regular and awe inspiring phenomenon, which gives cause for utmost care in introducing rigid instruments," and he did not "fructify," i.e., expand his experiments. It was the rhino-laryngologist Gustav Killian of Freiburg University who on June 4, 1895, attended Kirstein's lecture in Heidelberg at the second Congress of the Southern German Laryngologists, who immediately recognized the importance of Kirstein's observation for the diagnosis and treatment of laryngo-tracheal diseases and began his experiments with the new method.

In 1877, the urologist Nitze in Dresden and the instrument maker Leiter in Vienna together had constructed the first lens optic in which electrical illumination was performed by the glowing platinum wire at the distal end. It had to be cooled by a constant flow of water, such as in von Mikulicz' first gastroscope, when not used inside the urinary bladder. In 1879, T.A. Edison invented the electric bulb, which was further miniaturized by Mignon; distal electric illumination could be applied to endoscopes for inspection of the airways.

The Development of Local Anesthesia

In his first report on the invention of direct bronchoscopy Killian said: "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." Before the detection of cocaine, many attempts had been made to anesthesize the airways by the use of potassium-bromide, ammonia, belladonna, iodine solution, chloroform, morphine, and others. Nothing proved sufficient, and the patients had to be desensitized by weeks of rehearsing to touch the pharynx and the vocal chords by themselves before a procedure could be performed. The examiner had to be extremely skilled, and operations had to be performed within seconds before the view disappeared. Von Bruns advised training on an excised larynx and on a head that had been severed from a corpse and hung from a hook before training on a volunteer "…who certainly could be found rather easily for a little amount of money and would suffer such not really pleasant but not at all painful or dangerous experiments."

Although Morton in Boston had introduced general anesthesia by chloroform already in 1848, its use was so dangerous that it was only rarely applied in laryngoscopic operations. In 1882, a young scientist at the pharmacological institute of Vienna, Sigmund Freud, experimented with cocaine, a sample of which he had bought from Merck Co. He was eager to make a fortune by an important invention in science to impress and marry his fiancé. But to his later dismay his experiments in withdrawing morphinists from their addiction resulted in disaster. Although he had advised his colleague Koller, an eye specialist to use cocaine solution for pain relief when he suffered from severe conjunctivitis, he failed to recognize the importance of his observation himself that cocaine caused numbness when he put it to his tongue. Koller, however, immediately realized the immense potential of this observation and after feverishly experimenting with this new "miracle drug" on rabbits and patients inaugurated local anesthesia in his lecture on September 15, 1884, at the Annual Congress of German Ophthalmonologists in Heidelberg, Germany. At the same time the Viennese laryngologist Jellinek introduced cocaine as a local anesthetic for the inspection of the airways: "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." Thus the way was paved for Gustav Killian to pursue his experiments with bronchoscopy after he had attended Kirstein's lecture in Heidelberg.

Gustav Killian and the Invention of Bronchoscopy

Gustav Killian was born on June 2, 1860, at Mainz on the Rhine, Germany. After graduation from high school in 1878, he began to study medicine at the university of Strassburg where one of his teachers was Adolf Kussmaul. After 1880 he continued clinical education at Freiburg, Berlin, and Heidelberg where he passed his final examination in 1882. Afterward he started clinical work at the municipal hospital of Mannheim, Germany, close to Heidelberg and later in Berlin to get an education in ENT medicine by Hartmann and Fraenkel. As he could not find employment Killian settled down as a practitioner in Mannheim in 1887. Four months later, when his teacher in Freiburg, Germany, had died by an accident, he was offered to become the head of the section of rhino-laryngology at Freiburg, which was part of the large faculty of internal medicine, and he left Mannheim again. In Freiburg his scientific career started as a physician and pioneer began.

At the meeting of the Society of South German Laryngologists in Heidelberg in 1889, he gave a short report on a new technique for examination of the dorsal wall of the larynx. Killian learned about Kirstein's new technique at the meeting of the Society of South German Laryngologists in Heidelberg in 1895. Because of the experiences of Pieniazek at Krakau, who had introduced direct lower tracheoscopy via tracheostomy without any complications, Killian at once realized the potentials of this new method of direct inspection of the trachea and in 1896 began experimental work. In tracheotomized patients, he passed the bifurcation with the "bronchoscope," a somewhat modified esophagoscope of Rosenheim, and noticed that the bronchi were elastic and flexible and he was "stopped only when the diameter of the tube was surpassing that of the bronchi."

After he had confirmed his findings in frozen corpses without tracheotomies as well, he dared to perform the first direct endoscopy via the larynx in a volunteer. He noticed the flexibility of the trachea and how easy he could adjust it to the angle of the main bronchi and introduce the endoscope down to the lobar level. "I think I have made an important discovery" he noted afterward. Bronchoscopy was born. In 1897, he removed the first foreign body via the translaryngeal route, which his pupil Kollofrath reported in his paper.

After further experience and removal of two more foreign bodies, Killian felt safe to present his new method of "direct bronchoscopy" at the sixth meeting of the Society of South German Laryngologists at Heidelberg on May 29, 1898, and in the same year his first publication on direct bronchoscopy was published (Münchener Medicnische Wochenschrift No.27, July 5, 1898). The following years at Freiburg were full of technical improvements of the new method and with

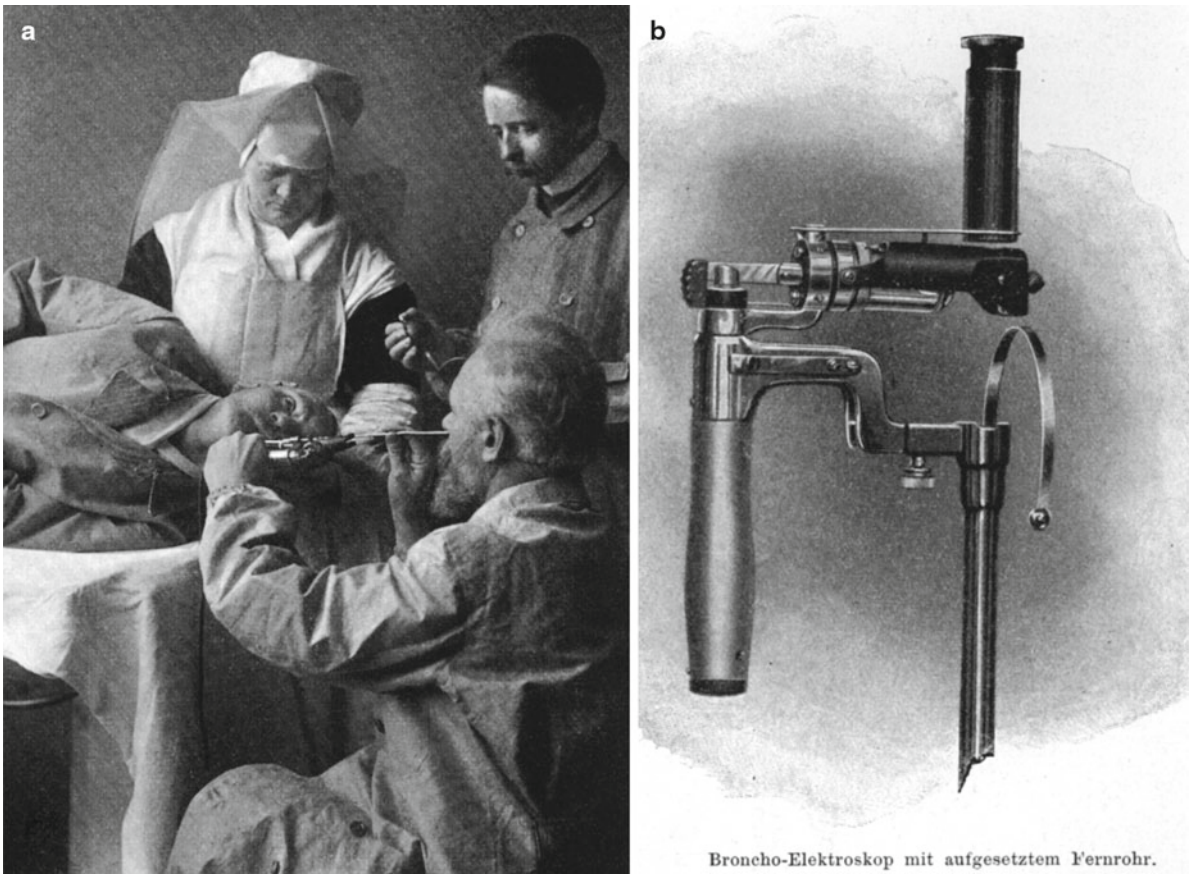

Fig. 1.1 Gustav Killian performing bronchoscopy. He is holding the bronchoscope with his left hand, while guiding a suction catheter with the right hand. His coworker is pumping the balloon for suctioning secretions, while the nurse is attending the patient, who is lying on his left side and has to tolerate the procedure under local anesthesia. (**a**) On the *right* is an illustration of the bronchoscope, modified by Killian's coworker Brünings. On the proximal end of the bronchoscope is a spring with a serrated edge, to which another tube could be attached and forwarded as far as necessary. Attached to the handle is Hacker's electroscope for illumination and onto that a telescope is mounted for enlarging the image (**b**)

the quest for more and more indications of its application (Fig. 1.1). He published 34 papers concerning discovery, technique, and clinical application of his invention. In 1900, he received the award of the Wiener Klinische Wochenschrift for his paper on "Bronchoscopy and its Application in Foreign Bodies of the Lung." Due to his publications and many lectures he was very famous, and Freiburg became the "Mekka" of bronchoscopy. Hundreds of physicians came from all over the world (the list of participants notes 437 foreign guests from all continents, more than 120 from the United States) and up to 20 training courses had to be held every year. He was invited as a very popular speaker all over Europe, and patients were sent to him from as far as South America for the removal of foreign bodies.

In order to fully understand the importance of endoscopic removal of foreign bodies, one has to consider the state of thoracic surgery at Killian's time. Most of the patients fell chronically ill after the aspiration of a foreign body, suffering from atelectasis, chronic pneumonia, and hemorrhage from which half of them died if left untreated. Surgical procedures were restricted to "pneumotomy" when the bronchus was occluded by extensive solid scar tissue, and the foreign body could not be reached by the bronchoscope, which had a very high mortality rate. Lobectomy or pneumonectomy could not be performed before Brunn and Lilienthal developed the surgical techniques after 1910, and Nissen, Cameron Haight, and Graham introduced pneumonectomy after 1930, because techniques of safe closure of the bronchial stump were missing.

Thus for those who were confronted with these patients it must have seemed like a miracle that already briefly after the introduction of bronchoscopy almost all patients could be cured. According to statistical analysis by Killian's coworker Albrecht, of 703 patients with aspiration of foreign bodies during the years 1911–1921, in all but 12 the foreign body could be removed bronchoscopically, although many had remained inside the airways for a considerable time, a success rate of 98.3%. In light of these results Killian's triumphant remarks become understandable when he writes: " One has to be witness, when a patient who feels himself

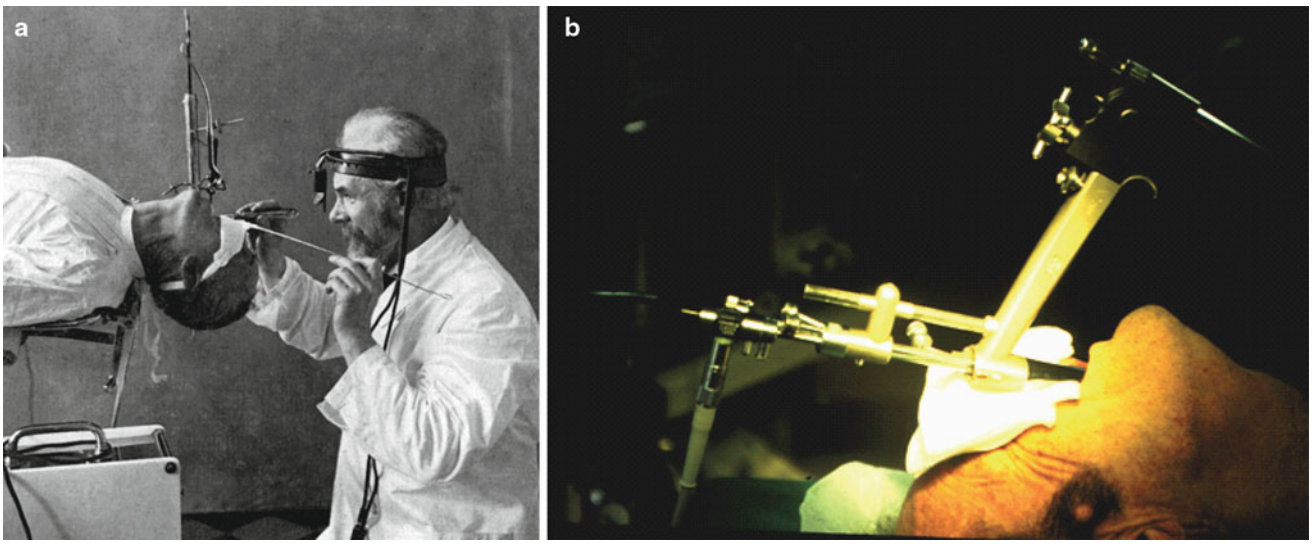

Fig. 1.2 Gustav Killian demonstrating suspension laryngo-bronchoscopy. The patient's head is suspended on a spatula that is fixed to a metal arm at the table. Illumination is provided by an electric head light, connected to the light source in the foreground by cable. Both hands are free for instrumentation. (**a**) Kleinsasser's support laryngoscope is a modern successor that is widely used by today's ENT surgeons. It rests on the chest of the patient or on a table. Microscopic telescopes and instruments for manipulation can be fixed directly to the device for delicate surgery on the vocal chords (**b**)

doomed to death can be saved by the simple procedure of introducing a tube with the help of a little cocaine. One must have had the experience of seeing a child that at 4 pm aspirated a little stone, and that, after the stone has been bronchoscopically removed at 6 pm, may happily return home at 8 pm after anesthesia has faded away. Even if bronchoscopy was ten times more difficult as it really is, we would have to perform it just for having these results."

Besides numerous instruments for foreign body extraction other devices, such as a dilator and even the first endobronchial stent, were constructed. Although further development of bronchoscopy was Killian's main interest, in the years at Freiburg he promoted treatment in other fields too. He developed a method for submucosal resection of the septum of the nose and a new technique for radical surgery of chronic empyemata of the sinuses with resection of the orbital roof and cover by an osseous flap. Around 1906, he began intensive studies of the anatomy and the function of the esophageal orifice and found the lower part of the m. cricopharyngeus to be the anatomical substrate of the upper esophageal sphincter. According to his observations it was between this lower horizontal part and the oblique upper part of the muscle that Zenkers pulsion diverticulum developed, where the muscular layer was thinnest. One of his scholars, Seiffert, later developed a method of endoscopic dissection of the membrane formed by the posterior wall of the diverticulum and the anterior wall of the esophagus.

In 1907, he received an invitation by the American Oto-Rhino-Laryngological Society to visit the United States, and it was on his triumphant journey through the United States on July 3, 1907, he gave a lecture on his findings at the meeting of the German Medical Society of New York, which was also published in *Laryngoscope* in the same year. Lectures were followed by practical demonstrations of his bronchoscopic and surgical techniques and by banquets at night. On his journey he also visited Washington, where he had a brief encounter with President Theodore Roosevelt. At Pittsburgh he met Chevalier Jackson, then already the outstanding pioneer of esophago-broncholgy at the University of Pennsylvania. Killian was awarded the first honorary membership of the Society of American Oto-Rhino-Laryngology and also became honorary member of the American Medical Association and received a medal in commemoration of his visit.

As Killian was the most famous laryngologist of Germany, when Fraenkel in Berlin retired in 1911 he became successor to the most important chair of rhino-laryngology. Although bronchoscopy seemed to have reached its peak, he felt that visualization of the larynx was unsatisfactory. When using Kirstein's spatula for drawing illustrations of pathological findings in corpses, once accidentally the head of a body slipped off the table. This was when Killian realized that inspection of the larynx in a hanging position of the head was much easier. He had a special laryngoscope constructed that could be fixed to a supporting construction by a hook, a technique he called "suspension-laryngoscopy," by which he could use both hands for manipulation (Fig. 1.2). His pupil Seiffert improved the method by using a chest rest, a technique that later was brought to its perfection by Kleinsasser and is still used for endolaryngeal microsurgery.

In 1911, Killian had been nominated Professor at the Kaiser-Wilhelm-Military-Academy of Medicine and as during World War I he had to treat many laryngeal injuries he visited the front line in France where he also met his two sons who were doing their military service. After his return he founded a center for the treatment of injuries of the larynx and the trachea. During this era he was very much concerned with plastic reconstruction of these organs, especially as he could refer to the work of Dieffenbach and Lexer, two of the most outstanding plastic surgeons at their times who had also worked at Berlin. The article on the injuries of the larynx should be his last scientific work before he died of gastric cancer in 1921.

During his last years, Killian prepared several publications on the history of laryngo-tracheo-bronchoscopy. For teaching purposes, already in 1893, he began illustrating his lectures by direct epidiascopic projection of the endoscopic image above the patient's head. Phantoms of the nose, the larynx, and the tracheobronchial tree were constructed according to his suggestions. According to his always cheerful mood he was called the "semper ridens" (always smiling), and in his later years, his head being framed by a tuft of white hair, his nick name was "Santa Claus." He created a school of laryngologists, and his pupils dominated the field of German laryngology and bronchology for years. Albrecht and Brünings published their textbook of direct endoscopy of the airways and esophagus in 1915. Like von Eicken at Erlangen and Berlin and Seiffert at Heidelberg they had become heads of the most important chairs of oto-rhino-laryngology in Germany. It was to his merit that the separate disciplines of rhino-laryngology and otology were combined. When Killian died on February 24, 1921, his ideas had spread around the world. Everywhere skilled endoscopists developed new techniques, and bronchoscopy became a standard procedure in diagnosis and treatment of the airways. His work was the basis for the new discipline of anesthesiology as well, providing the idea and instruments (laryngoscope by Macintosh) for the access to the airways, endotracheal intubation, and anesthesia.

Throughout all his professional life Gustav Killian kept on improving and inventing new instruments and looking for new applications. He applied fluoroscopy, which had been detected by K. Roentgen in Würzburg in 1895, for probing peripheral lesions and foreign bodies. To establish the X-ray anatomy of the segmental bronchi he introduced bismuth powder. He drained pulmonary abscesses and instilled drugs for clearance via the bronchial route and he even used the bronchoscope for "pleuroscopy" (thoracoscopy) and transthoracic "pneumoscopy," when abscesses had drained externally. Foreign bodies that had been in place for a long time and had been imbedded by extensive granulations were successfully extracted after treatment of the stenosis by a metallic dilator and in case of restenosis metallic or rubber tubes were introduced as stents. Although cancer was comparatively rare (31 primary and 135 secondary cancers disease in 11,000 postmortems), he pointed out the importance of pre- and postoperative bronchoscopy. Already in 1914, he described endoluminal radiotherapy in cancer of the larynx by mesothorium, and in the textbook of his coworkers Albrecht und Brünings published in 1915, we find the first description of successful curation of a tracheal carcinoma after endoluminal brachy-radiotherapy. Taking special interest in teaching his students and assistants to maintain high standards in quality management by constantly analyzing the results of their work and always keeping in mind that he himself was standing on the shoulders of excellent pioneers, he kept up the tradition of the most excellent in his profession like Billroth of Vienna. In his inaugural lecture in Berlin on November 2, 1911, he pointed out that it was internal medicine from which the art of medicine had spread to the other faculties and that patience and empathy should be the main features of a physician, but on the other hand to persist in following your dreams because "to live means to be a fighter". He ignited the flame of enthusiasm in hundreds of his contemporaries who spread the technique to other specialties thus founding the roots for contemporary interventional procedures like microsurgery of the larynx (Kleinsasser) and intubation anesthesia (Macintosh, Melzer, and Kuhn).

Rigid Bronchoscopy in the Twentieth Century

Main Schools

Due to the enthusiastic activities of Killian and his assistants in teaching and spreading the new technique, hundreds of specialists all over the world were educated in performing bronchoscopy, and many improvements were added to the instrument. Thus, by 1910, Killian had collected 1,116 papers – 410 on esophagoscopy, 34 on gastroscopy, and 672 on laryngo-tracheobronchoscopy – for his paper on the history of bronchoscopy and esophagoscopy. Back then it was almost impossible to follow all traits in every continent where soon after the introduction by pioneers separate schools developed.

Killian's coworkers von Eicken, Albrecht, Brünings, Seiffert, and others for decades held the chairs of all important departments in Germany. They improved Killian's instruments and introduced new methods such as endoscopic treatment of Zenker's diverticulum by Seiffert, who also developed the chest rest for laryngoscopy (1922), which was perfected by Kleinsasser to the current device for microlaryngoscopy (1964). Unfortunately after World War II the development took separate ways until recently. In Western Germany Huzly in Stuttgart was the most prominent

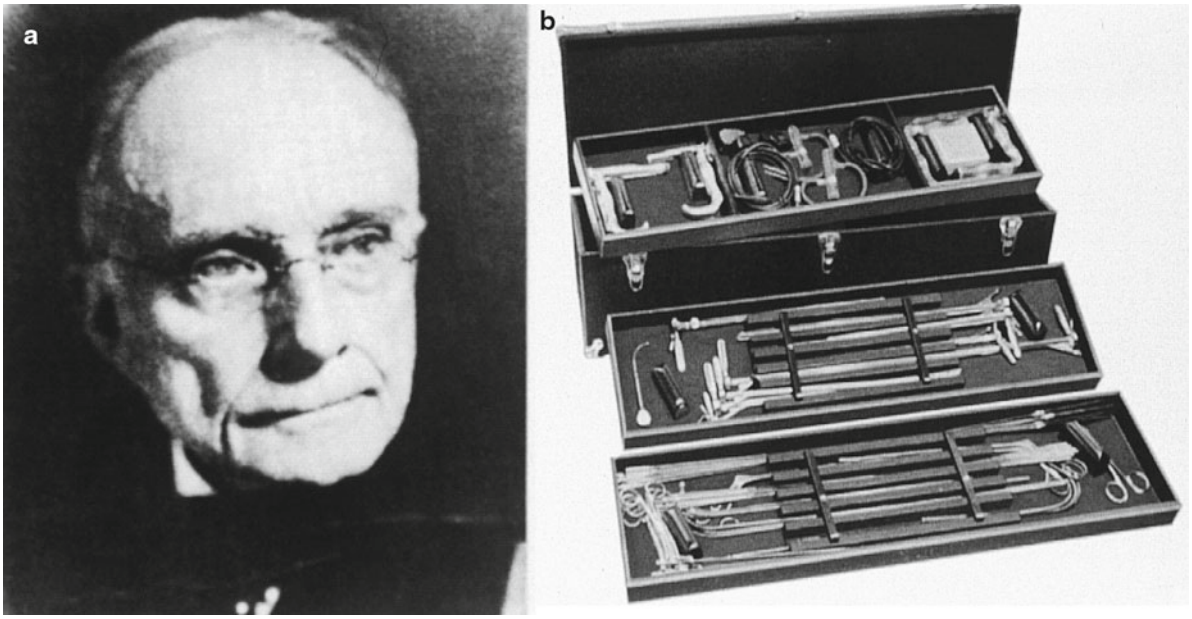

Fig. 1.3 Chevalier Jackson, the pioneer of rigid bronchoscopy in the United States (**a**) with a case of bronchoscopes and accessories in a carrying case, made by the instrument makers Pillings and Sons Co. (**b**)

proponent of rigid bronchoscopy who in 1961 edited his photographic atlas of bronchoscopy. Riecker introduced relaxation by curare in 1952, which was replaced by succinylcholine by Mündnich and Hoflehner in 1953. Maassen introduced bronchography via double lumen catheter in 1956. Two companies, Storz and Wolf, became the most important instrument makers in Germany and introduced new technologies such as the Hopkins telescope and television cameras. In the late twentieth century, Dierkesmann, Freitag, Häußinger, Macha, and Becker in Germany were the proponents of rigid bronchoscopy for the development and performance of interventional procedures such as laser treatment, stenting, and photodynamic laser therapy. In East Germany, Friedel developed the first ventilation bronchoscope (1956) which was modified by Brandt (1963), who edited an extensive textbook on endoscopy of the air and food passages in 1985, in which he reported on more than 100 successful treatments by endobronchial stenting which he already began in the early 1970s. In the same year as E. Schiepatti of Buenos Aires wrote about transtracheal puncture (TBNA) of the carinal lymph nodes, Euler reported on pulmonary and aortic angiography by transbronchial puncture in 1948/1949 and later on the technique of rigid TBNA for mediastinal masses in 1955 which was further perfected by Schießle in 1962. Cavaliere in Italy, Diaz-Jimaneez in Spain, and Dumon in France became the forerunners in Nd-YAG laser treatment via the rigid bronchoscope, and Dumon developed the first widely applied stent with a special application device. Also he invented a dedicated therapeutic rigid bronchoscope.

In the United States, when A. Coolidge on May 11, 1898, performed the first lower tracheo-bronchoscopy at the Mass. General Hospital, it was Chevalier Jackson in Philadelphia, whom Killian had met on his visit to the United States in 1907, who together with his instrument maker Pillings made many improvements in instruments for bronchoscopy and esophagoscopy and became the "father of American bronchoesophagology." During his training to become laryngologist he had visited London in 1886 where he was shown the "impractical device designed by Morel Mackenzie in an effort visually to inspect the esophagus". In 1890, he constructed the first endoscope "worthy of the name" for esophagoscopy and in 1904 he constructed the first American bronchoscope. After Einhorn in New York had added an integrated light conductor and Fletcher Ingals of Chicago had introduced distal illumination to the esophagoscope, Jackson equipped his bronchoscope with a light carrier with a miniaturized electric Mignon bulb at the distal end and with an additional suction channel. Confronted by many patients suffering from aspiration of foreign bodies he invented many instruments for its removal. In 1907, he published the first systematic textbook on bronchoesophagology which he dedicated to Gustav Killian, the "father of bronchoscopy" (Fig. 1.3). In this book he already addressed modern issues

of quality management such as analysis and prevention of complications and rational construction of bronchoscopy suites and arrangement of equipment and staff. Being a thorough philanthropist he constantly refused to have his inventions patented as he wanted them to be spread as widely as possible, and by his persistence in negotiating with the government, he promoted a law for the prevention of accidents by ingestion of caustic agents. He was a perfectionist in techniques and totally convinced that teaching had to be performed on animals before treating patients. Therefore he always refused to go back to England where animal rights activists prevented such training courses. In 1928, in recognition of his "conspicuous achievements in the broad field of surgical science," he was awarded the Bigelow Medal by the Boston Surgical Society which was presented to him by H. Cushing "for his eminent performances and creative power by which he opened new fields of endeavor" and in acknowledgement of his "indefinable greatness of personality." He simultaneously held five chairs of laryngology at different hospitals in his hometown Pittsburgh and Philadelphia. His son Ch. L. Jackson also became laryngologist and was his successor at the Temple University of Philadelphia. He became the founder of the Pan American Association of Oto-Rhino-Laryngology and Bronchology and of the International Bronchoesophagological Society and Co-founder of the World Medical Association. Together with his father he edited the last issue of the textbook.

Their school extends well into our time as many of today's specialists' teachers were trained by the Jacksons, such as E. Broyles in Baltimore, who after additional training by Haslinger in Vienna introduced the telescope optic for bronchoscopy in 1940, the optical forceps in 1948, and fiber illumination for the rigid bronchoscope in 1962. His scholar G. Tucker became professor at Jefferson in Philadelphia where he trained B. Marsh who kept the tradition into our days together with Ch. M. Norris. P. Hollinger and Brubaker who became specialists in pediatric bronchoscopy and introduced color photography in the 1940s. Hollinger's son became a famous pediatric laryngologist. Andersen at Mayo Clinic was the first to perform bronchoscopic transbronchial lung biopsy via the rigid bronchoscope in 1965. Sanders in 1967 introduced jet-ventilation for rigid bronchoscopy.

After staying with Killian in Freiburg Inokichi Kubo of Kyushu University in Fukuoka first introduced bronchoscopy to *Japan* in 1907. He was joined by S. Chiba who after training with Brünings stayed in Tokyo from 1910. Joe Ono who was trained by Jackson in 1934 founded the Japan Bronchoesophagological Society in 1949. Shigeto Ikeda who later developed the flexible fiberscope introduced glass fiber illumination for the rigid bronchoscope in 1962. When Ikeda, who found rigid bronchoscopy under local anesthesia in the sitting position on "Killian's chair" cumbersome, introduced the flexible bronchoscope he still used it in combination with a flexible tube that could be straightened by a locking mechanism so that he was still able to introduce the rigid optic in the same session. In the era of expanding interventional procedures, this method of combining both the rigid and the flexible endoscope regained new attention and became widely spread.

Technical Developments

Illumination

After the advent of the electrical bulb, illumination became sufficient for the illumination of the airways. At first the lamps were installed separately on statives or fixed to a head rest from where the light was reflected into the endoscope. Connection of the light source to the endoscope improved handling considerably. Thus Killian and his coworkers preferred to use Casper's panelectroscope in which the light bulb was integrated into the handle from where it was reflected by a prism to the endoscope because it was not so easily soiled by secretions. Jackson, however, used distal illumination via a light guide with a Mignon bulb at its tip. Already in the late 1880s von Schrötter in Vienna developed a rigid light guide made of Plexiglass which was improved by the introduction of quartz by K. Storz. After Tyndall's first description of the optical properties of glass fibers in 1872, patents for glass fibers as transport medium were almost simultaneously given to Baird in England (1926), Hansell in the USA (1927), and Marconi in England (1930). The first prototype of a fiberscope was presented by Lamm in Munich (1930). After Hansen in Denmark described the first fiber bundles for light transportation in 1930, Van Heel in the Netherlands and O'Brian in the USA developed the first endoscopes for bronchoscopy and gastroscopy in 1953 and 1954. The rod lens and fiberoptic lighting device by Hopkins in London were adopted by K. Storz as cold light illumination source for his rigid endoscopes in 1963. The transition to fully flexible endoscopes with image transport by glass fibers was performed by Hirschowitz and ACMI in 1958 after Curtiss of Ann Arbor had described the first medical fiber instrument in 1955.

Photo-, Film- and Videodocumentation

The first (even stereoscopic) endophotographies were performed by Czermak by the use of a giant laryngeal mirror. Stein in Frankfurt used magnesia illumination for his photographic apparatus, the "heliopictor" ca. 1875, technically the predecessor of the Polaroid-Land camera of 100 years later. Stein's camera was improved by Nitze and Kollmann.

In 1907 Benda introduced color photography which was first introduced by P. Hollinger to bronchoscopy in 1941. Soulas (1949) and Hollinger (1956) also introduced endoscopic film documentation. The first television transmission of a bronchoscopy was performed by Dubois de Monternaud in 1955. Wittmoser constructed an angulated optic for the improvement of image transfer and produced the first video documentation in 1969.

Prospect

With the advent of the flexible bronchoscope after 1966, two developments took place: bronchoscopy rapidly spread beyond oto-rhino-laryngological and specialized thoracic clinics, and the overall number of rigid bronchoscopies declined rapidly until the late 1980s and early 1990s because bronchoscopy had become much easier. But then again, the increasing number of interventional techniques demanded use of the rigid bronchoscope for safety reasons (Fig. 1.4). Special rigid devices were developed by J.F. Dumon for the application of the Nd-YAG-laser and placement of his "dedicated stent" (Fig. 1.5) and by L. Freitag for his "dynamic stent." Consensus task forces of the Scientific Section of Endoscopy of German Society for Pulmonology, of the ERS/ATS, and of American College of Chest Physicians agreed that for many interventional procedures the bronchoscopist and staff should at least be trained in the technique of rigid bronchoscopy and should have the instrument at hand in case of an emergency. Thus, in training courses all over the world handling of the rigid instrument is taught again and future developments are on the horizon (Fig. 1.6).

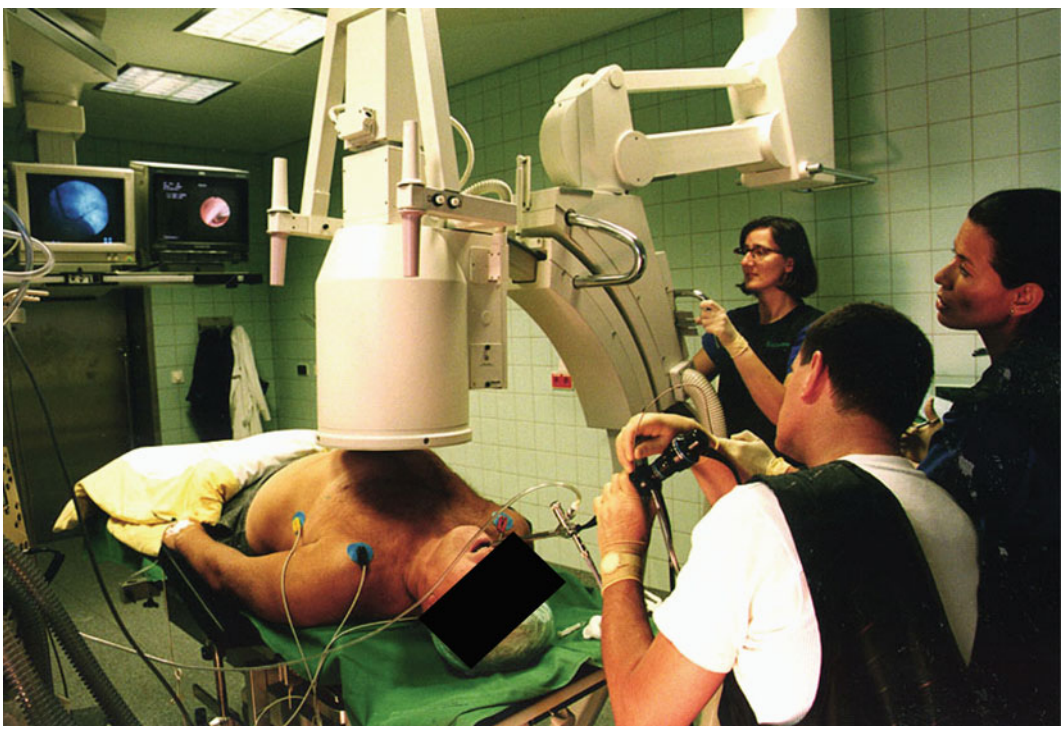

Fig. 1.4 Modern bronchoscopy suite. The bronchoscopist inserts the flexible scope via the rigid bronchoscope for easy manipulation of the biopsy forceps inside the periphery of the airways. Visual control by two monitors, on which the endoscopic and fluoroscopic images can be followed by all the staff for guiding the C-arm and handling of the forceps. At the proximal end of the rigid bronchoscope the jet catheter for ventilation and the glass fiber light cable are attached. The patient is monitored by ECG, pulse oximetry, and automatic blood pressure control

Fig. 1.5 J.F. Dumon (standing on the *left side*, besides the author) (**a**) and his dedicated bronchoscope for intervention (Efer-Dumon). At the entrance port it has three channels for suction and instrumentation and side ports for jet- or conventional ventilation. At the distal end in front end of the telescope optic are two bendable channels for insertion of laser or APC probes and suction (**b**)

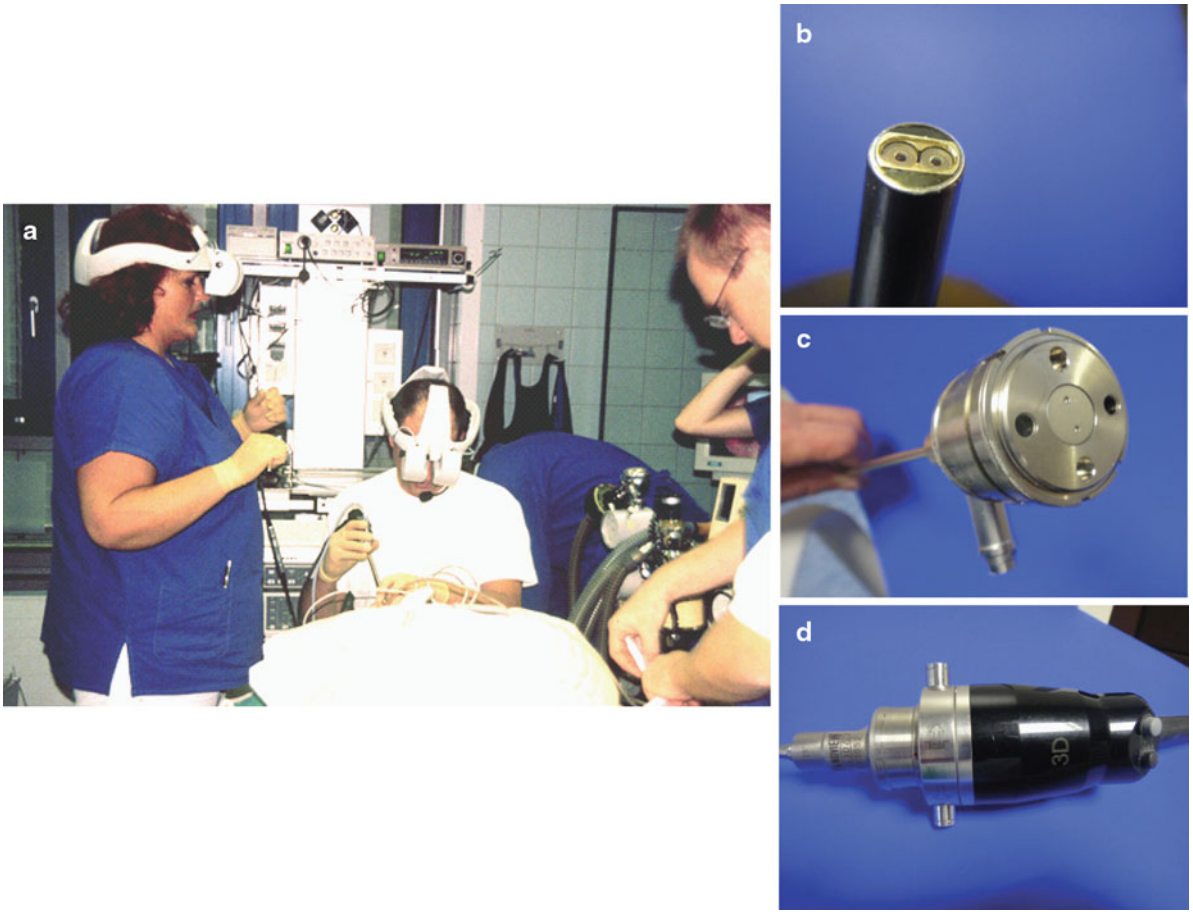

Fig. 1.6 Prototype of a 3D rigid bronchoscope (Panoview, Wolf Co, Knittlingen, Germany). (**a**) The images of two separate lens systems in the telescope optic (**b**) are picked up by a camera head with two chips at the proximal end of the optic. (**c**, **d**) Via a processor they are transferred to head mounted devices (HMD) that have separate monitors for each eye, giving a 3D image of the airways. Each participant in the procedure has to wear a device in order to see the endoscopic image that cannot be displayed on external monitors

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General Principles of Endoscopic Imaging

2

Harald W. Dremel

Introduction

The easy and safe access to image acquisition of the bronchial tract has been a long-standing desire of many physicians. Yet, the technical challenges faced while delivering images of the bronchi are much tougher than in many other endoluminal disciplines like gastroenterology. The anatomical structures of the bronchi require a thin, flexible endoscope shaft to reach desired deep structures in the periphery as well, while the wish to obtain biopsy specimen supporting the diagnosis or the need for retrieval of a foreign body demands a working channel and thus a wider diameter.

Retrospectively, it was a windy and stony road. Gustav Killian's first successful removal of a foreign body under direct visualisation using a rigid instrument in 1897 marked a very important milestone. Shigeto Ikeda's vision of the design of a flexible fibre bronchoscope in the late 1960s of the twentieth century was another major breakthrough for bronchoscopy procedures globally. Today's flexible bronchoscope technology utilising video chip technology and special light for better differentiation and contrast of pathological changes builds the actual cutting edge of this development. The story continues. This chapter will give an overview of the evolution of the first idea of a flexible bronchoscope to current state-of-the-art video bronchoscopy design, technology highlights in endoscopic imaging and design to finally providing an outlook to further improvements arising at the horizon.

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The Idea of a Flexible Bronchoscope

It was Shigeto Ikeda's visionary approach to hand over technical specification sheets in parallel to two Japanese endoscope manufacturers, requesting the development of a flexible bronchoscope. In spring of the year 1964, Ikeda handed over the idea with specifications of his flexible bronchoscope (see Table 2.1) to Machida Endoscopic Company Ltd. and Olympus Optical Company Ltd. in Japan.

The companies started to work on the implementation resulting in two slightly differing realisations as outcome of this competition. The first prototype of Machida was shown to the public in summer 1966 – without working channel and limited angulation. The seventh version was finally the one to become commercially available under the name Machida One in 1967. Olympus worked in parallel and manufactured a first prototype in August 1966 under the model name Olympus No 1. During the year 1967–1968, several design modifications improved the handling and specifications remarkably. These years can be considered as the starting point of flexible fibre bronchoscopes finding their way into the pulmonary departments worldwide.

Evolution of Flexible Bronchoscope Design

A fast penetration contributed to a swift gathering of valuable early adopters' feedback. The experience from specialised respiratory centres proved to be a solid basis for advice on how to further enhance the bronchoscope. In the following years, bronchoscopes were already available in a variation of different models (see Fig. 2.1), targeting different applications.

The first bronchoscopes were based on fundamental technology available for gastroenterologists for examination of the GI tract (see Fig. 2.2). The major technical challenge was the required thinner flexible shaft of the bronchoscope.

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It had to accommodate a sufficient number of glass fibres to transport the light into the lumen, a high precision fibre bundle to transport the image from the distal end of the scope to the eyepiece. Via the ocular piece at the proximal end, the physician can observe the area of interest. The proximal tip of the bronchoscope can be angulated by a lever which is located at the control section – the central part of the scope the user is holding and manoeuvring the scope with. Different to GI scopes which usually allow deflection of the distal tip in all four directions (up/down, left/right), the bronchoscope can be bent only in two directions 180°and 130°, respectively. A measure to safe space, as such a strategy requires only two wires to run inside the shaft. By clockwise or counterclockwise shaft rotation, the bronchoscope tip can reach all areas of interest. A working channel, sometimes called instrument channel, provides aspiration possibilities and guides thin long instruments, so-called endotherapy devices, to, e.g. acquire specimen during the procedure, allowing subsequent histopathological examination.

Imaging Fibre Bundle

The imaging fibre bundle is a key component of a flexible fibre bronchoscope and determines the image quality. The clearer and more well defined the image quality, the more support it delivers to the diagnosis of the lesion and suggests options for further treatment planning. The challenge is that each single fibre has exactly the same dimension and is positioned at the identical position at both ends of the fibre bundle. If this is not achieved, the image quality is impaired and artefacts disturb the image (see Fig. 2.3).

Table 2.1 Requested specifications of the first flexible bronchoscope

Outer diameter	<6 mm
Imaging fibre bundle	
Single fibre diameter	<15 μm
Number of fibres	>15,000
Focus	5–30 mm
Angulation of distal end	60 ° at 30 mm from distal end
Length of the rigid part of distal end	<10 mm
Total length	~1 m
Field of view	80 °, prograde

Channel System Inside the Fibre Bronchoscope

For various purposes, channels are running through the bronchoscope. The first one is starting at the control section down to the distal tip. It is used for aspiration of mucous – and consequently called suction channel. A suction valve at the control section is connected via a tube to an external suction pump. By pushing this valve, the bronchoscopist can activate the suction function. Slightly deeper at the lower part of the control section, a second port is available, the so-called instrument channel port. Through a different valve at this port, endotherapy instruments can be inserted into the bronchoscope to reach the lesion of interest inside the bronchial tract. Thus allowing, e.g. to guide biopsy forceps and to retrieve specimen for further investigation. Sometimes, it is therefore also called biopsy channel. As a space-saving measure, the instrument channel joins the suction channel at the lower part of the control section.

Light Source

In addition to the bronchoscope, the user needs a light source which delivers the light along the glass fibre bundles down to the lumen of interest. The bronchoscope is connected to the device while the examiner is observing the illuminated lumen through the eyepiece (see Fig. 2.4).

Fig. 2.1 Three early bronchoscope models with different outer diameter (Olympus)

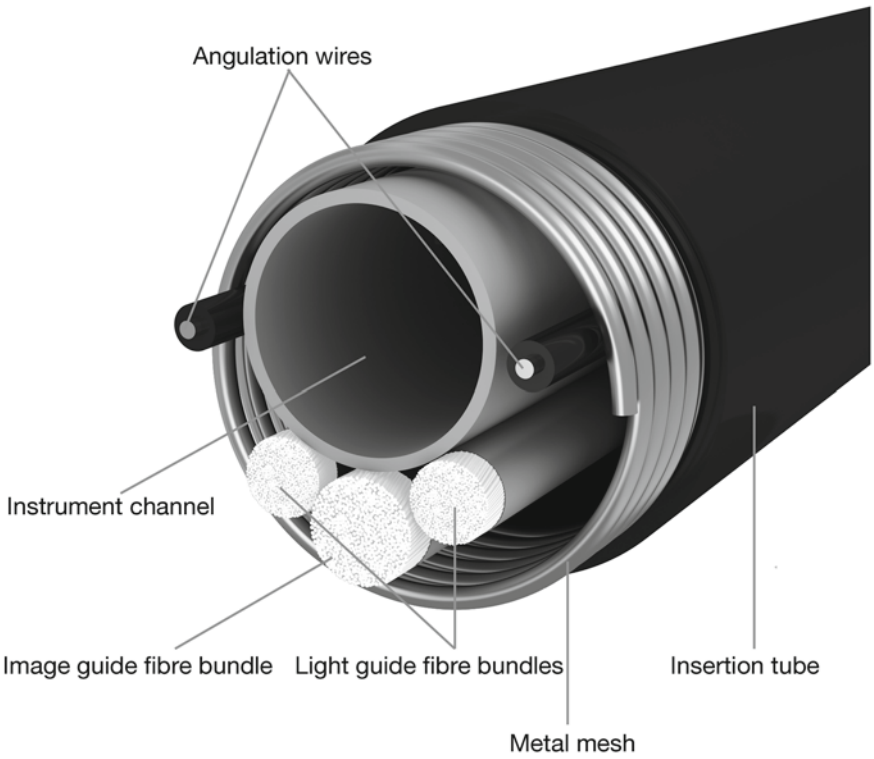

Fig. 2.2 Details of the internal arrangement of components

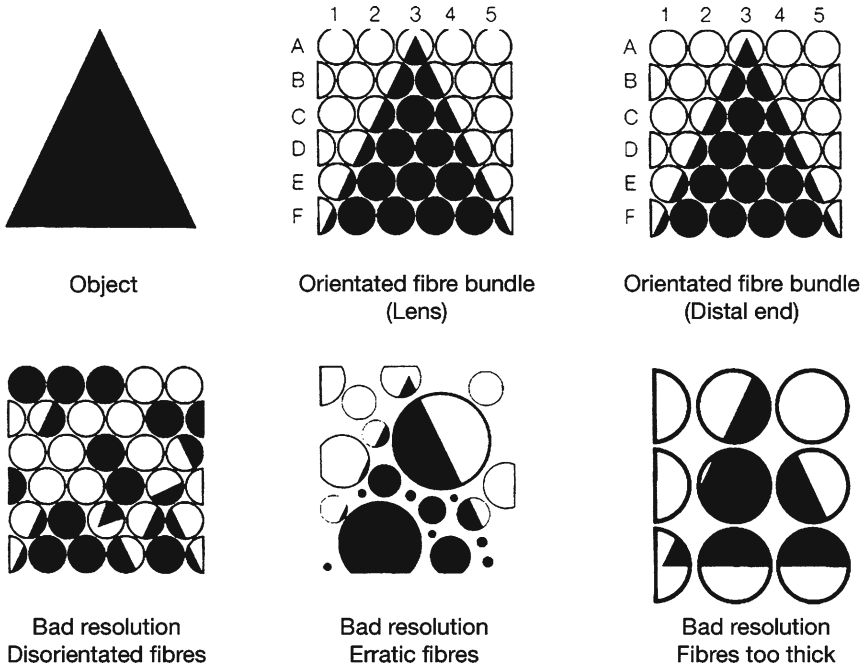

Fig. 2.3 Importance of fibre bundle arrangements

Suction Pump

Finally, to complete the system, a pump is required which is connected to the suction channel connector. In case the examiner is activating the valve at the control section, visibility interfering mucous can be aspirated through the channel system to clear the view.

Principles of Airway Image Acquisition

Over decades, a wide range of fibre bronchoscopes have been in use in daily routine. The continuous advances in endoscopy design and especially the introduction of video technology – a key breakthrough and a quantum leap for the image quality – influenced the bronchoscope evolution (see Fig. 2.5).

Fig. 2.4 Principle design of a fibre bronchoscope

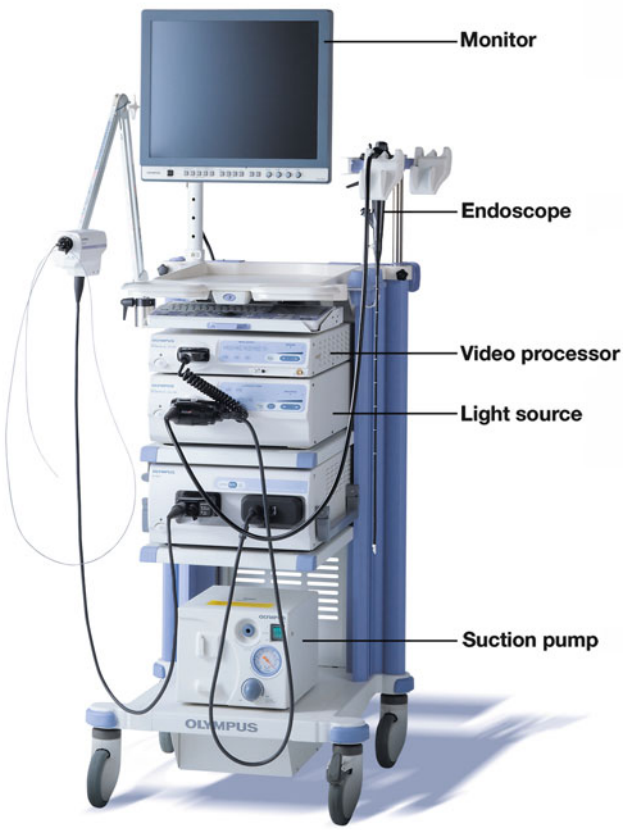

Fig. 2.5 Example of a complete modern endoscopic system

The core component needed is the CCD chip (charged coupled device) which delivers as a light-sensitive analogue device the image as a electrical signal and is mounted at the distal tip just behind a lens system (see Fig. 2.6).

The major technical challenge was the miniaturisation of the CCD chip enough that the human anatomy can accommodate the outer shaft dimension of such a video bronchoscope. In comparison to a fibre scope, the image glass fibre bundle requires less space compared to the CCD sensor. The eyepiece though is no longer necessary. Wires deliver the electrical video signal to the light guide connector (see Fig. 2.7).

In addition to the light source, a video processing unit is now mandatory. After looping the signal through a connection to the video processor with relevant signal processing measures, the user observes the endoluminal image on a monitor linked to the video processor (see Fig. 2.8).

Two Fundamentally Different Acquisition Technologies

Since the very first design concepts of video bronchoscopes, there existed two different principles of image acquisition by video signal. The key difference is the way how the CCD sensor at the distal tip of the endoscope is working and acquiring the image contents information in detail.

One principle is using pure white light and the CCD sensor is converting the reflected white light from the bronchus

Fig. 2.6 Internal arrangements of lenses and CCD in the scope distal section

Fig. 2.7 Handle and light guide/image connector of a modern video bronchoscope

into video signal components. Active image sensor areas, called pixels, produce the signal for red (R), green (G) and blue (B) portion. One pixel for each colour simultaneously. It is therefore called colour chip system. The other principle follows a different methodology in how to compose the RGB colour information. Instead of simultaneous image detection, the light produced in the light source is transmitted through a rotary RGB filter wheel, resulting in short revolving sequences of R, G and B light. The difference is that 1 pixel is responding on the colour sequences and delivering the R-G-B components of the image sequentially. The system is therefore called R-G-B sequential or sometimes (misleadingly) black and white system (see Fig. 2.9).

Both systems have advantages (see Table 2.2). R-G-B sequential CCDs can be designed in smaller dimensions, and this was the first system utilised for video bronchoscopes. Later, when the technology advancement allowed further miniaturisation, colour chip CCDs found their way into the tip of video bronchoscopes. The advantage of this technology is that even fast movements do not disturb the image by the so-called rainbow effect, an effect resulting from the fact that while the scope is moving fast the system does not have "enough time" to collect all three-colour signals. The consequence is a small band of false colours. The latest technology is reducing this effect, but the principle itself might hardly allow a complete elimination. The colour chip system established itself well in USA and continental Europe. Japan and UK in contrast focus on the RGB sequential system.

Autofluorescence Imaging (AFI)

While the step from fibre scopes to video scopes realised an unprecedented advancement in endoscopic imaging quality, the desire to facilitate improved detection possibilities, especially the detection of early lesion, still leaves room for improvement. An approach to use special light is autofluorescence imaging. White light endoscopy is utilising visible light of differing wave lengths between 380 (purple) and 720 nm (red) (see Fig. 2.10). AFI utilises the inherent properties of short wavelength blue light (390–470 nm) to assess mucosal tissue (see Fig. 2.11).

When the blue excitation light reaches the subepithelial layer, healthy tissue will fluoresce green. However, if there is any subtle mucosal change in the surface layer, potentially consistent with early malignant change, such as increased vasculature or thickening of the mucosa, tissue fluorescence will decrease. Therefore, by enabling changes in florescence to be observed, AFI can assist the early detection of suspicious lesions, displaying normal tissue in green and abnormal in magenta (see Figs. 2.12 and 2.13).

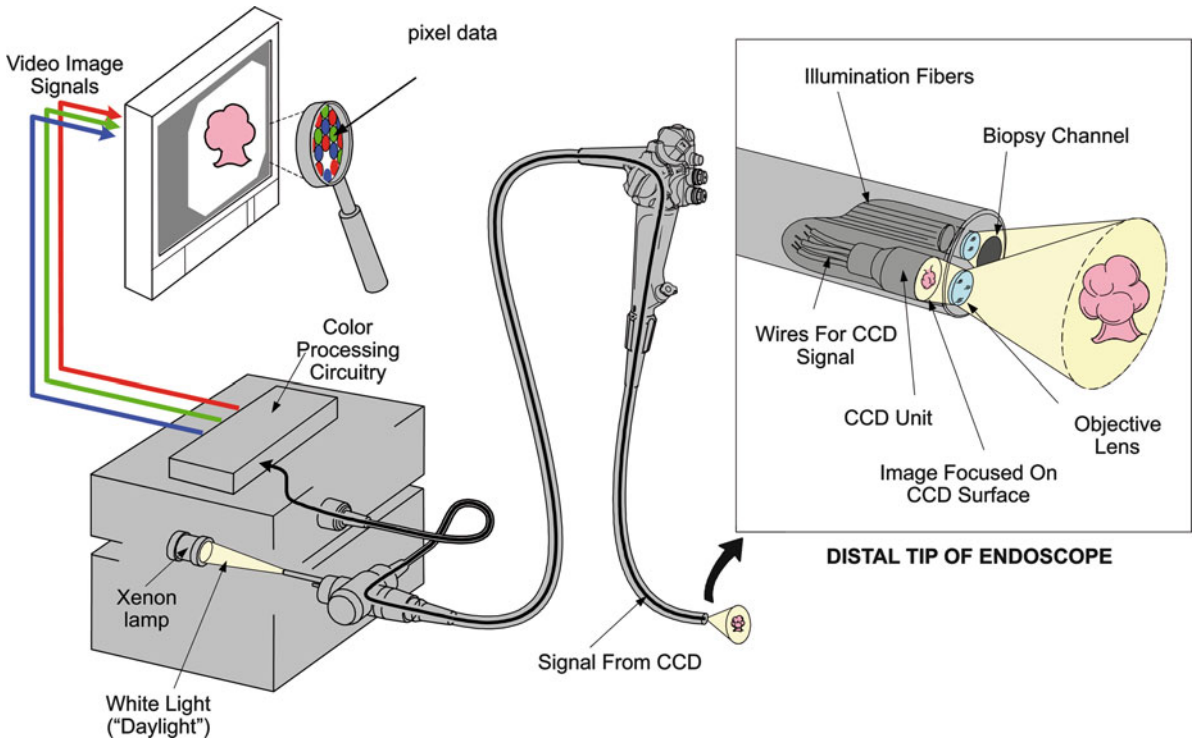

Fig. 2.8 System design of modern video endoscopy

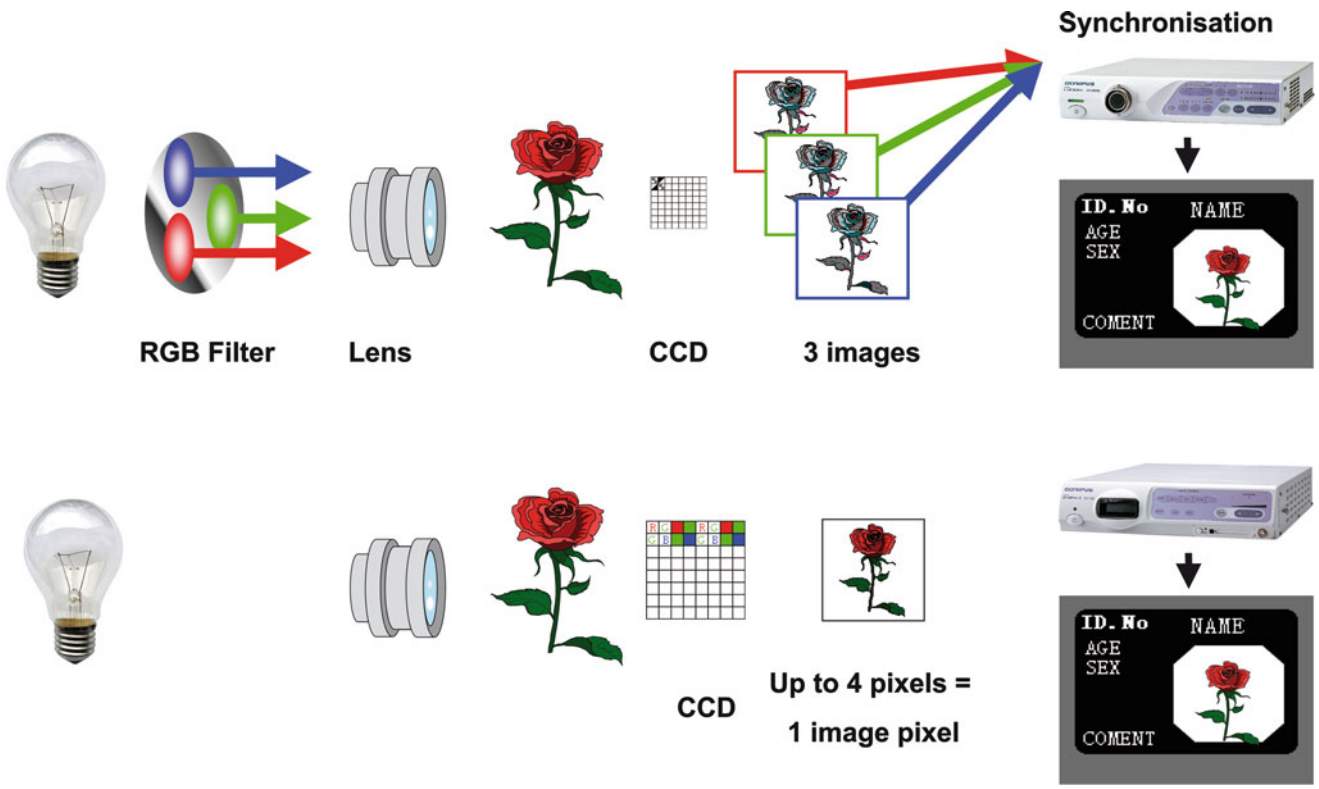

Fig. 2.9 Principles of RGB sequential (top) and colour chip (bottom) image generation

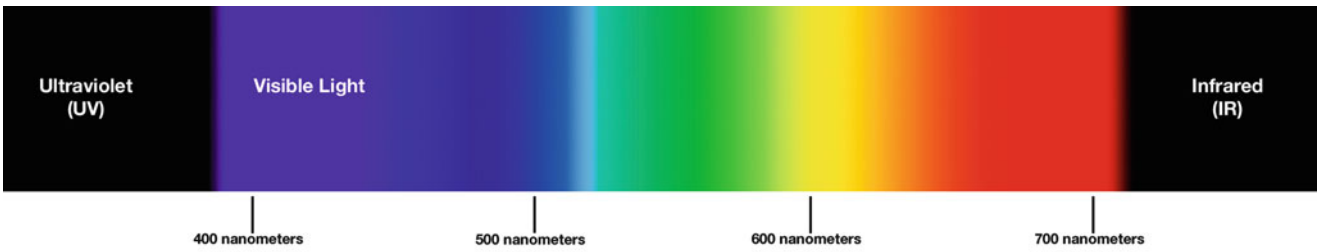

Fig. 2.10 Spectrum of light

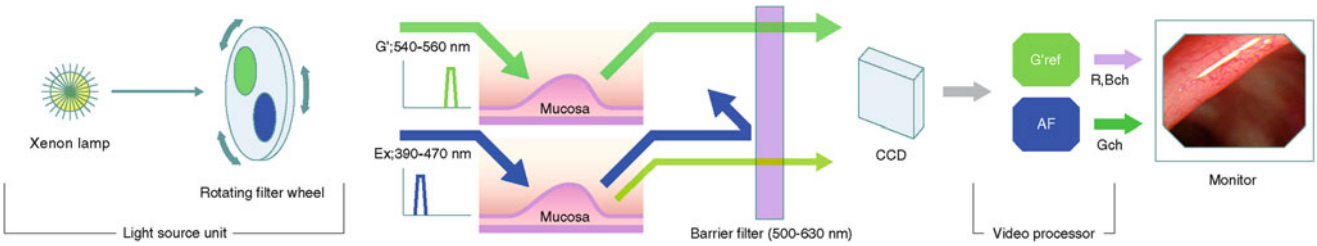

Fig. 2.11 Principle of autofluorescence imaging technology

Table 2.2 Key advantages of RGB sequential and colour chip technologies

RGB sequential	Colour chip
Small outer dimensions	Easier design of light source
Natural colour (no colour filters)	Easier image processing
Higher resolution (at given dimensions)	No rainbow effect

The technical challenge is, compared to white light endoscopy, the need for the special CCD to detect the extremely low intensity autofluorescence light signal.

AFI bronchoscopes therefore utilise two different CCD chip sensors: One used for standard white light endoscopy imaging and the other hypersensitive one whenever the AFI image mode is selected (see Fig. 2.14).

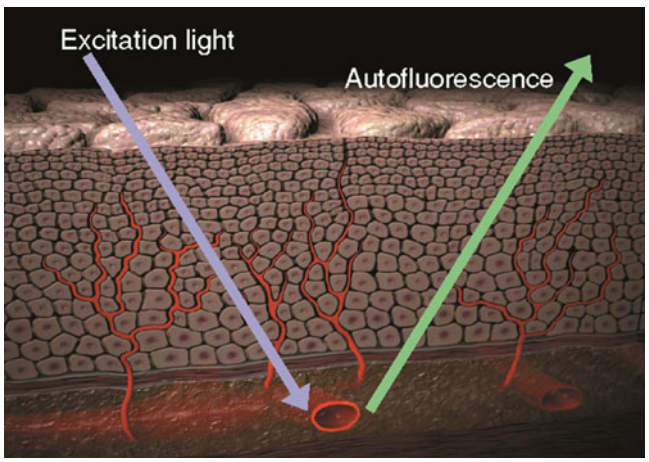

Fig. 2.12 Autofluorescence and the mucosa

Narrow Band Imaging (NBI)

Another approach of special light observation is making use of scattering and absorption properties of human tissue. The penetration depth before being scattered (partly absorbed) depends on the wavelength (colour) of the light. The shorter the wavelength (e.g. blue), the earlier it is reflected. Longer wavelengths (e.g. green) penetrate deeper. In other words, the image obtained through white light is a composition of slightly different tissue layers (see Fig. 2.15). A bright but partially blurred image is the result.

Narrow band imaging (NBI) enhances the visualisation of the capillary network and mucosal morphology during endoscopic observation of the gastrointestinal tract.

Via a button at the control section, the NBI mode is activated. A rotary filter moved into the light beam and alters the

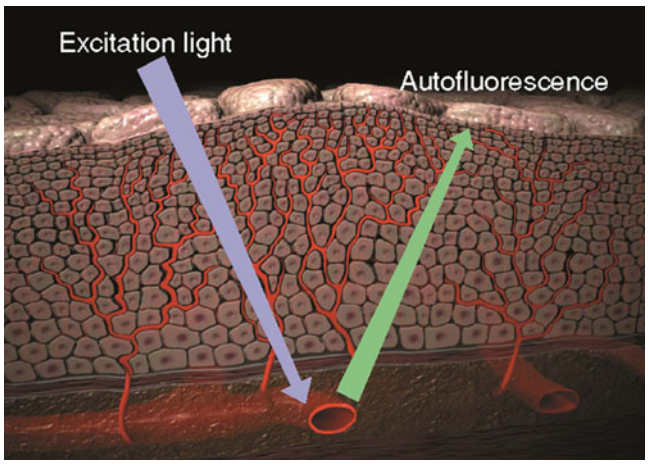

Fig. 2.13 Autofluorescence and the mucosa

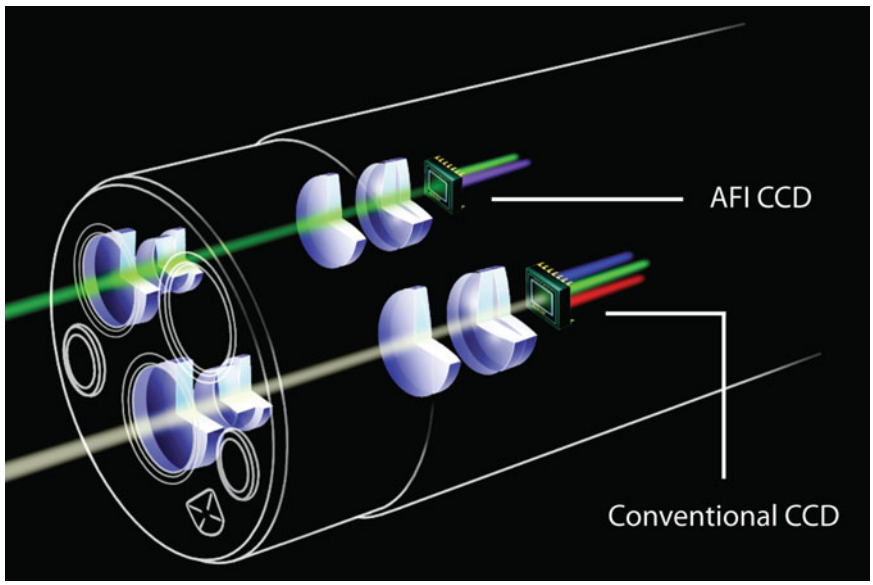

Fig. 2.14 Internal design of AFI scopes

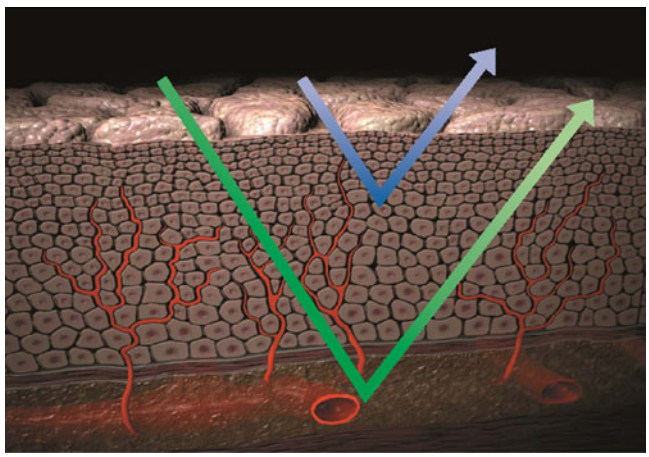

Fig. 2.15 Different wavelength light and the mucosa

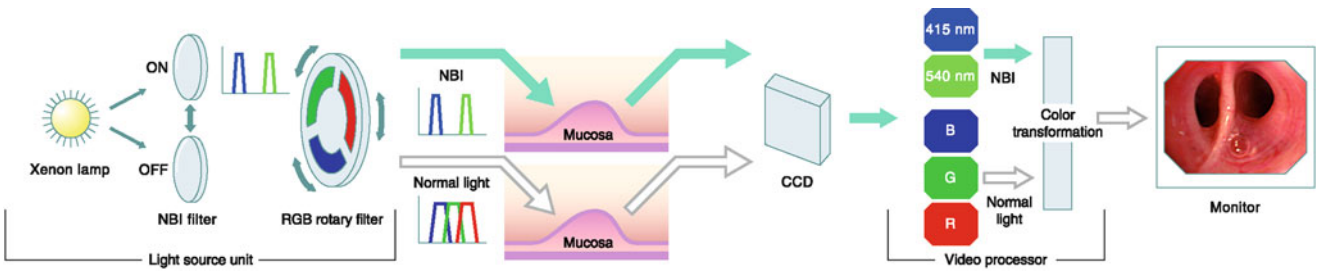

Fig. 2.16 Principle of narrow band imaging technology

white light to consist of specific wavelength bands (blue 415 nm and green 540 nm). The endoluminal observation is now done with this special light composition (see Fig. 2.16).

The result is an image with focus on superficial mucous layers (blue) and the capillary network of the deeper submucosal layer (green). This provides improved visual contrast of the surface structure and fine capillary patterns of the mucous membranes. The fact that only selected bandwidths are emitted results in a lower brightness which requires special high-sensitive dual mode CCDs. Recent systems try to achieve such high contrast image depiction from post-processing using special software algorithms. In any case, the user can select the mode by a switch on the control section of the bronchoscope.

Hybrid Fibre-Video Bronchoscopes

The pursuit to reach more peripheral lesions requires extremely thin insertion tube diameter of bronchoscopes. A new concept incorporates a modified endoscope design strategy. It unifies the advantages of thin calibre fibre scopes and the better image quality and easier image recording features of video scopes. The CCD is removed from the distal tip and placed in the control section. A thin glass fibre bundle is delivering the image from the distal tip to the CCD. The control section offers enough space to accommodate the image fibre bundle – CCD interface link (see Fig. 2.17).

The result is, e.g., a 4-mm-outer-diameter bronchoscope featuring a 2-mm working channel. The design combines the ergonomic handling of a video scope with a small outer diameter but still providing a wide working channel. The image quality is superior to pure fibre scopes image; furthermore, the video signal can be visualised on a monitor and also be recorded. The limitation from the fibre bundle as original starting point of the image acquisition remains. Another phenomenon which can occur over time is that single fibres can break. A broken fibre loses its capability to transport the light from one end to the other. This wear-and-tear effect can affect light guide bundles and image bundles over years. While the light intensity is impacted in the first case, for the latter case, little black dots in the image are the result.

Mobile Fibre Bronchoscopes

Technical advancement in the field of light-emitting diodes (LED) led recently to the availability of super bright miniaturised LEDs which can be incorporated in the distal tip of an endoscope. The low power consumption allows operating LEDs with batteries over hours. In combination with a small monitor attached (e.g. a display known from digital consumer cameras), a design of a lightweight mobile bronchoscopes is possible (see Fig. 2.18). Instead of the traditional eyepiece, the tilt- and rotatable monitor can be used to observe the surface of the bronchi or alternatively to review recorded images or video clips (see Table 2.3). The flexible usability during emergency cases or in the ICU is now easier possible with such scopes, requiring a charged battery pack and an optional memory card which can record the medical findings during the procedure.

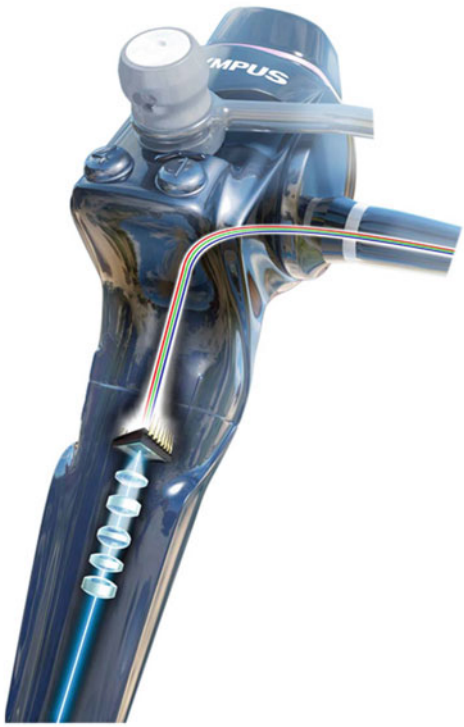

Fig. 2.17 Placement of the CCD inside the control section of a hybrid scope

Fig. 2.18 Mobile fibre bronchoscope

Table 2.3 Specifications of a mobile bronchoscope

Mobile scope specifications	
Supply voltage	3.7 V
Current consumption	350 mA
Maximum battery life	60 min (rechargeable)
Frames/images per second	15 (video mode)
	30 (still images)
Still image max. size	1,600 × 1,200 pixels
Movie max. size	640 × 480 pixels

Outlook

Future technology advancements in miniaturising CCD chip technology will open up the chance to integrate high-definition, so-called HDTV, CCD image sensors in the distal tip. While current standard definition video signals deliver 475 or 575 vertical lines (NTSC/PAL standard) as active image resolution, the recently introduced HDTV standard is composed of 1,080 lines in vertical direction. The overall image will contain more minute details for a potentially better diagnosis of the mucosa.

Reprocessing of Bronchoscopes and Autoclaving

The very first bronchoscopes were not at all watertight. Which means reprocessing of these first models needed special attention and lots of manual work. Hygiene awareness and standards were getting stricter over the years, so the bronchoscope design needed to be consequently enhanced in this respect as well. A breakthrough in this endeavour was the first completely watertight bronchoscope. Since then, it is possible to completely immerse the scope in cleaning and disinfection solution during the manual, semi-automatic or nowadays automatic reprocessing procedure. The disinfection chemicals base either on glutaraldehyde or recently more and more on peracetic acid.

Considerations to further enhance the safety of cross-contamination between patients have resulted in the request to design a flexible bronchoscope which can be autoclaved, e.g., in the central sterilisation department of a hospital. Autoclaving is a routine procedure in hospitals to prepare, e.g., OR instruments for the next patient with temperatures of 134 °C and in France even 138 °C. The thermal stress to a flexible endoscope is huge. Various components consisting of different material undergo different expansion processes during the autoclaving procedure. A standard scope undergoing autoclave cycles shows deterioration at the universal cord, the insertion tube and at the light guide connector (see Figs. 2.19 and 2.20).

Fig. 2.19 Wearing and erosion through autoclaving of normal endoscopes

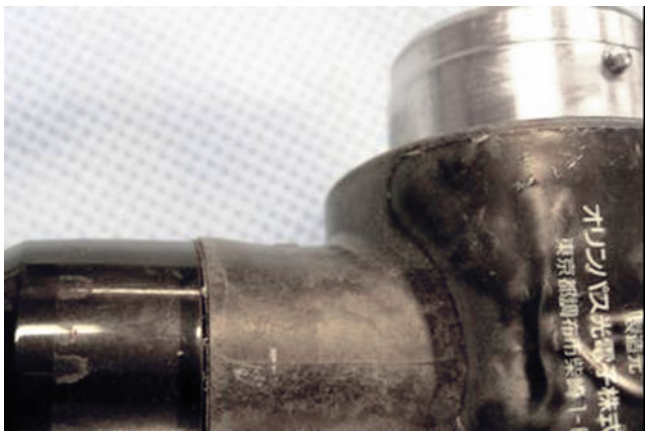

Fig. 2.20 Wearing and erosion through autoclaving of normal endoscopes

Typical sensitive areas and problems which are affected the most after several reprocessing cycles of a non-autoclavable endoscope are fog of the endoscopic view due to invasion of water creating humidity, cracks of the bending rubber, breaking of the top coating of the insertion tube, transformation and breaking of the control body. Without special preparation and careful material selection of those components, the endoscope will not withstand the reprocessing cycles and the endoscope will be damaged. Consequently, components formerly being glued together like the objective lens and the light guide lens had to be re-engineered. The revised design needs to allow different parts to be soldered together; thus, a high-tech metal coating of the lenses is necessary. Other components needed to be exchanged with biocompatible and heat-resistant material, which is repeatedly withstanding the thermal stress. Keeping the various components and materials used in a flexible bronchoscope in mind, only a solution for all challenges guaranteed the final autoclaving compatibility.

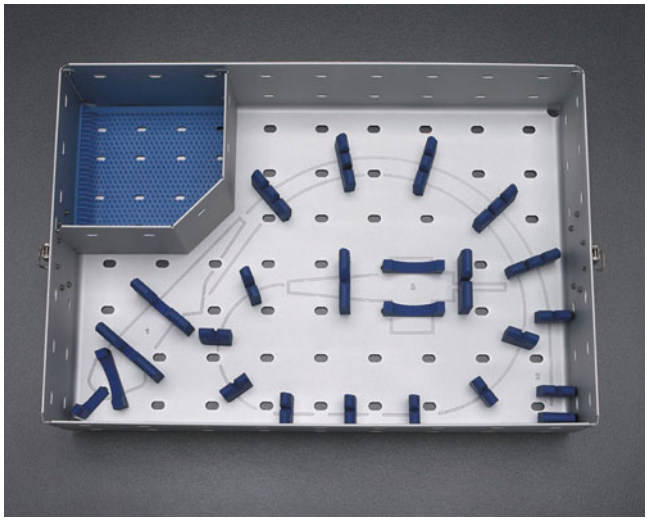

Fig. 2.21 Autoclave reprocessing tray

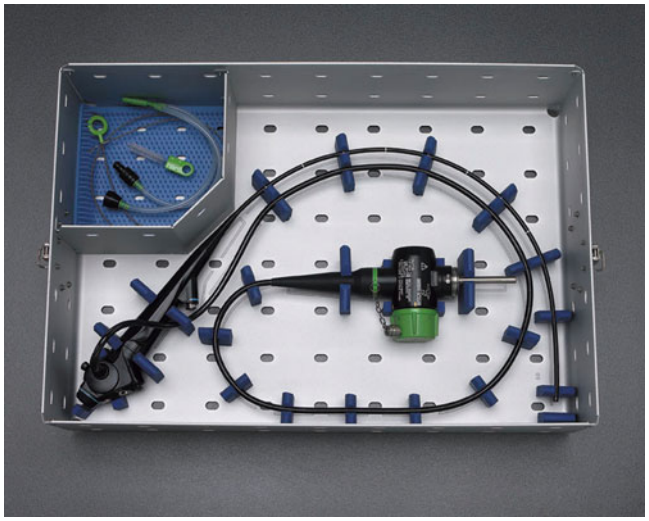

Fig. 2.22 Autoclave reprocessing tray

In order to ensure a standardised reprocessing result and to reduce the deformation of the flexible endoscope during autoclaving, a special reprocessing tray has been developed (see Figs. 2.21 and 2.22).

Acknowledgement All pictures used in this chapter courtesy and copyright of Olympus Medical Systems Corp., Tokyo.

Suggested Reading

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3 The Bronchoscope: What is Available, Determining Selection, and How to Properly Care for the Instrument

Robert Garland

Types of Bronchoscopes

The types of bronchoscopes currently available to the endoscopist can be divided into the purpose they were created for. The most logical way to view scopes might be to categorize them based on these three options listed below.

"Video Versus Non-video" Bronchoscopes

We should differentiate between bronchoscopes first by the way we view the object we are looking at. The principles behind how they work (and perform) vary tremendously and are perceived as the difference between the "old" and the "new" types of bronchoscopes. These two scopes are either "non-video" or "video" scopes.

In defining the bronchoscope of today, we must consider where we have come from in terms of the way images were created in the past. The use of flexible fiber-optic bundles allowed the first fiber-optic bronchoscope to be introduced in 1966. The ability of these bundles to reflect light and optical images while being bent allowed an instrument to be created which could "see around corners." This was the first time that an operator could look into the windpipe of a patient and see further than the main stem bronchi. This "*non-video*" bronchoscope (Fig. 3.1) allowed visualization to a single operator through the eyepiece at the top of the instrument.

The true "*video*" bronchoscope (Fig. 3.1) did not become available until 1987 when the charged coupled device technology (CCD chip) was able to be miniaturized to a point that it could be used in the endoscope. This advancement allowed tremendous improvements in image quality as well as the ability to integrate the imaging into a monitor for others to view.

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While the majority of bronchoscopes being produced today are true video scopes, there are still isolated instances where space limitations require fiber-optic bundles be used through most of the bronchoscope for image creation. This "hybrid" bronchoscope utilizes a combination of video and non-video technology to provide an improved image over a true fiber-optic system.

An example of this hybrid technology is the current bronchoscope with an ultrasound transducer built into the distal end used to view mediastinal lymph nodes (Fig. 3.2). Because of the size of the transducer, there is not enough space to also place a CCD chip for optimum imaging, so the insertion tube has a fiber-optic bundle used to transmit the image to a point in the control head where there is enough space to place a CCD chip. Until the technology is advanced to create a CCD chip small enough, fiber-optic technology is used to assist in providing imaging. Here is a good example of the development of a "new" type of bronchoscope which relies in part on the "old" non-video technology for its imaging.

The Size of the Bronchoscope

Since most bronchoscopes all perform basic functions allowing the operator to navigate the airways under direct vision and allow for sampling and video documentation, then the difference are the functions that the operator feels are needed to their specific patient population. Probably the biggest factor to consider is the size of the scope you may need. There are two factors to consider here: one is the outer diameter of the scope (insertion tube) and the other is the size of the working channel (the channel that accessories are placed for either sampling or treating). One would assume that there should be a direct relationship between the two, but that is not always the case. Sometimes, a scope will have to compromise the size of the working channel to allow for another technology to use some of that space. There are two examples that come to mind. One is the case of the dedicated ultrasound bronchoscope. The outer diameter of the scope is as large as one could

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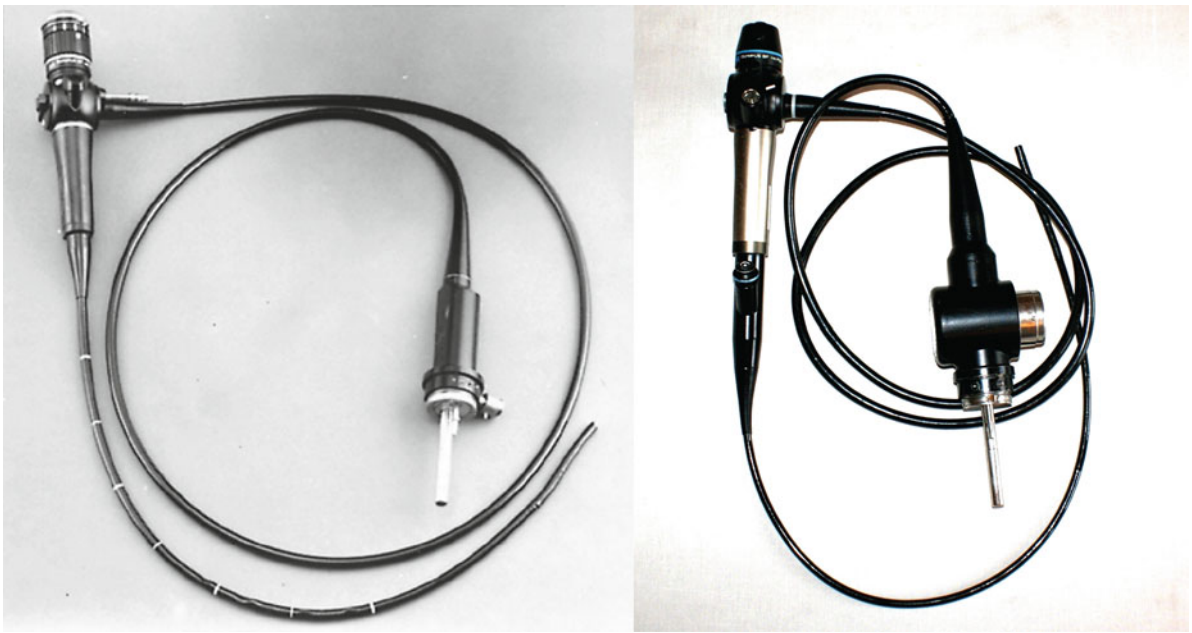

Fig. 3.1 Non-video and video bronchoscopes

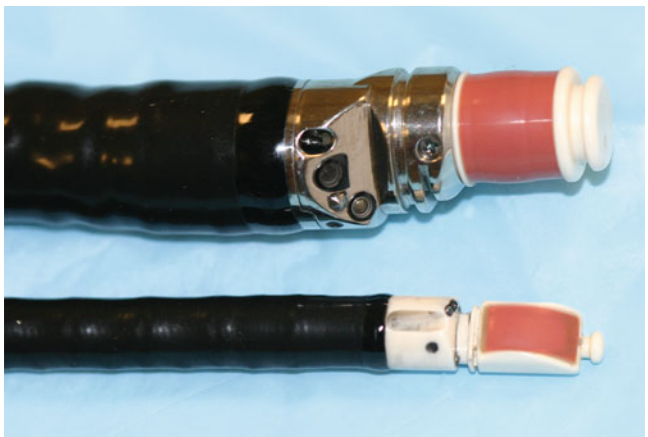

Fig. 3.2 Ultrasound endoscopes

Fig. 3.3 Variations in the size of bronchoscopes

probably make a scope to fit through the vocal cords of an adult, yet the working channel is that of only a standard scope (2 mm). That is because the ultrasound transducer has to take up much of the extra space in the insertion tube. The other is the case of a decision of the manufacturer to optimize the video capacity of the scope by using the largest CCD possible, but by doing that, we are left with a somewhat compromised working channel. It is up to the end user to determine in this case what is more important for their practice; the best possible imaging or a larger working channel.

The smallest scopes available (pediatric or ultrathin bronchoscopes) have an outer diameter of around 3 mm, and those that have working channels are a bit over 1 mm. The largest scopes (therapeutic bronchoscopes) have diameters approaching 7 mm with working channels somewhat over 3 mm (Fig. 3.3).

The difference between 1 mm in the working channel may not seem significant, but when you have an accessory tool that occupies 1.8 mm in a channel that is only 2.0 mm, there is no room to apply suction should your field of view become obscured, forcing you to remove the tool and start all over again. For the interventional pulmonologist, having the largest working channel can be a great friend and make for faster and safer procedures.

A Particular Function that the Bronchoscope May Provide

Over the past several years, there has been an explosion in technology development for the interventional pulmonologist. Much of this development is directed toward accessories placed through the working channel aimed at assisting the endoscopist in navigating through the airways, improving their diagnostic yield or providing better therapeutic options. Examples include electromagnetic navigation, alveoloscopy, and optical coherence tomography. Some of these technologies are still in their development stages and are not quite ready for clinical applications.

But there have also been developments to the bronchoscope itself. Newer technologies allow for integrated systems using the same bronchoscope to provide information using either different light frequencies to detect abnormal lung tissue (narrow band imaging, Fig. 3.4, or autofluorescence examination) and even the use of ultrasound technology to view through the airways themselves into the mediastinum to allow for sampling of these areas.

Efforts have been made to overcome the loss of suctioning ability when a large accessory tool has been placed in the working channel by designing scopes with a second working channel. But because of space limitations to the overall size of the bronchoscope, efforts to make this working channel large enough to be helpful have not been very successful.

Concerns over cross infection of patients undergoing bronchoscopy have prompted some manufacturers to develop bronchoscopes that can be steam sterilized and others that have a single use sterile sheath that can be placed over the entire scope (Fig. 3.5). The initial designs of these sheaths were cumbersome and very costly, but recent improvements seem very promising.

We are now just beginning to see high-definition bronchoscopes come to the market, and they are truly incredible. Because of the difference in size between bronchoscopes and gastroenterology scopes, it has taken a while longer for this technology to become available as our peers in gastroenterology have had this technology for several years. One must also remember that as the saying goes: "you are only as

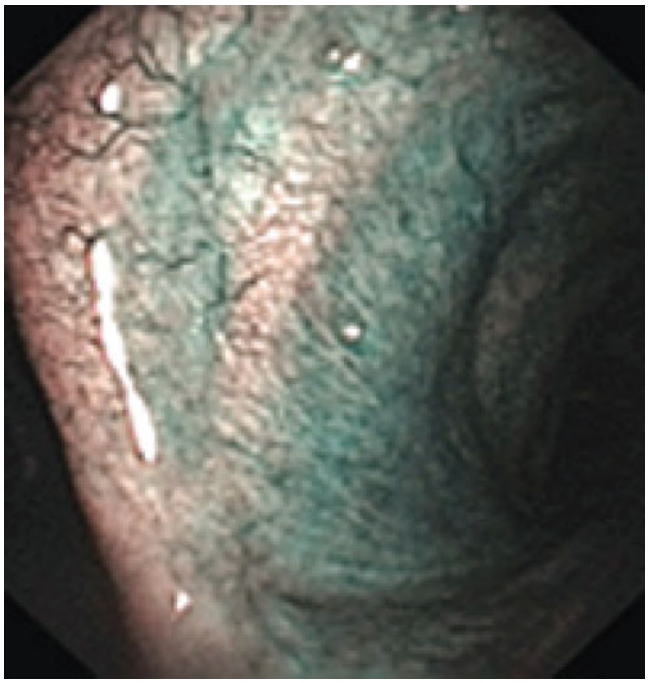

Fig. 3.4 Narrow band imaging

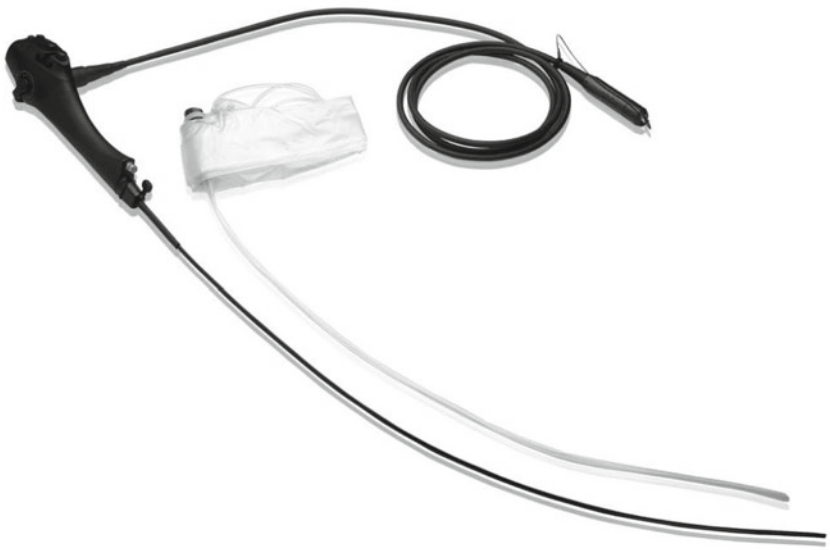

Fig. 3.5 Sterile sheathed bronchoscope

strong as the weakest link." This also holds true to the world of high definition. You cannot expect to get the proper imaging from these scopes without proper high-definition monitoring, processing, and cabling.

As technologies emerge to assist the endoscopist in navigating to peripheral areas of the lung that are unable to be visualized directly, one would expect the manufacturers themselves to develop their own "extendable working channel" and not have to rely on add-on systems to provide this function.

This cascade of technology development over the past several years should continue if reimbursement can be established for these modalities. But, to date, there has not been much success in providing payment for any of these, and this certainly will affect future development.

Determining Selection

When considering the purchase of a bronchoscope, one needs to consider whether you are adding to your current inventory or beginning a new program. Even if starting fresh, you will no doubt have an inventory of some bronchoscopes that are being used by others performing bronchoscopy procedures that you will have access to. It is highly unlikely, in this economic environment, that the administration will grant a blank check and not consider the value of those older but still functional scopes. That being said, the IP program director needs to compile a list of the number, size, and type of scopes necessary to maintain a proper inventory. There are many factors that one must consider when determining how many scopes a program needs, including but not limited to:

1. Current volume of procedures and growth over the first 3–5 years.
2. Types of patients you see and plan on seeing. (This will determine the size and types of the scopes you will need to purchase.)
3. Staffing patterns – This will determine the volume of patients you can handle.
4. Current and future reprocessing methods – To determine turnaround time for the availability of scopes.
5. Locations of procedures being performed – If procedures are performed in multiple locations at the same time, there may be less scopes available.

There are a variety of styles and sizes of bronchoscopes available for purchase. Most perform similar functions in that they allow the operator to visualize the conducting airways by using four integrated systems all contained in a plastic tube that is no more than a half inch in diameter.

1. ***Image System*** – Responsible for transmitting the image from a lens at the end of the scope back to a video processor where the image is displayed on a monitor (Fig. 3.6a).

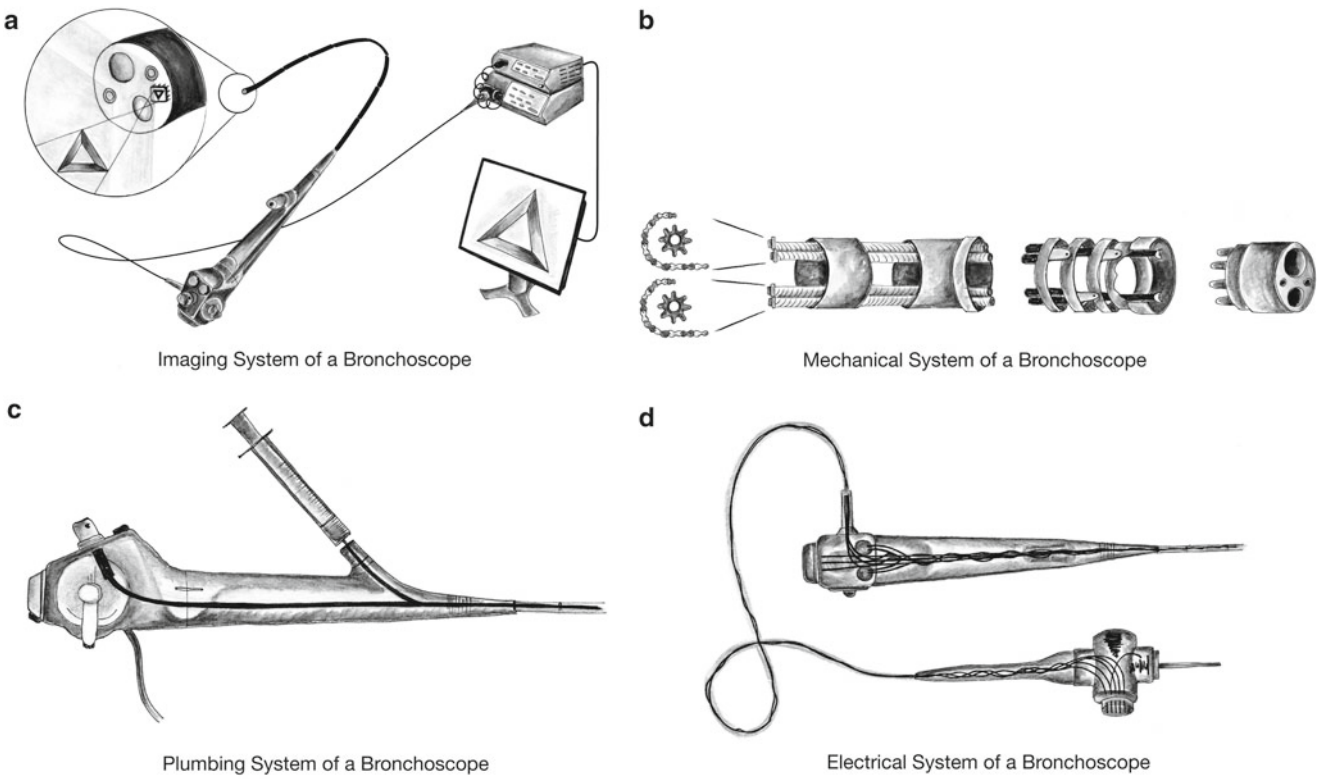

Fig. 3.6 Bronchoscopy systems

2. ***Mechanical System*** – Allows navigation through the airways via a system of levers, wires, and hinged metal bands (Fig. 3.6b).
3. ***Plumbing System*** – The working channel provides a communication between the upper end of the instrument and the distal end of the scope to allow for removal of blood or fluid to allow for proper viewing (Fig. 3.6c).
4. ***Electrical System*** – Provides for a light system to illuminate the airway so that navigation can take place. Also allows for operator to perform functions using remote buttons on scope like image capture or changing light exposure to the tissue (Fig. 3.6d).

Proper Care of the Bronchoscope in an IP Program

Conventional Bronchoscopy Versus Interventional Pulmonology

Proper care of the bronchoscope and the resultant prevention of damage will have great financial implications as well as implications for the overall success of an interventional pulmonology program. Let us first consider the differences between an interventional and a conventional bronchoscopy program.

The work performed in conventional bronchoscopy is usually related more toward the diagnosis of disease and not the treatment or therapeutic intervention of that process. Much of the "diagnosis" consists of sampling the airway by washing, brushing, or removing small bits of tissue with a biopsy forceps. Even the use of needle aspiration for mediastinal lymph node biopsies is sometimes looked upon as advanced procedures by conventional bronchoscopists.

The accessory tools used by the interventional bronchoscopist carry with them a much higher risk of damage to the bronchoscope itself. Specialized training in the use of these tools in preventing damage to the bronchoscope is critical to the success of the interventional program.

Damage to any form of an endoscope can be costly, but damage to the bronchoscope can be especially so, for two reasons.

First, the size of the bronchoscope is limited to the size of the space it has to pass, so it is very difficult to navigate through the vocal cords and see much more than the central airways with a scope larger than 6–7 mm in diameter. Because of this size limitation, the working parts of the bronchoscope are much smaller and therefore more delicate than, for instance, a gastroscope.

The other reason for more costly repairs is the nature of the development of interventional pulmonology itself over the past several years. Academic programs have been graduating fellows at an increasing pace because of the demand by hospitals to develop their own interventional programs. Industry has been trying to keep pace with this demand by producing technologies to meet the demand of physicians for improved products as well as the development of new technologies. Because of these reasons, academic centers have been inundated with new equipment to pass through the bronchoscope. Much of this equipment is either very sharp or pass extreme heat, cold, or electrical current through them to perform their role in assisting in the diagnosis or treatment of diseased tissue.

One other major difference that may lead to increased damage for the interventional pulmonology program compared to our counterparts in the gastroenterology field is the use of the rigid bronchoscope itself. In programs that perform rigid bronchoscopy as part of their armamentarium, the flexible bronchoscope is passed through the working channel of the rigid scope (Fig. 3.7a), so the rigid scope acts as a trocar for easy passage of the flexible scope and other accessories (Fig. 3.7b). This additional tool which is intended on making the life of the endoscopist easier and the life of the patient safer has its own reasons for increased risk of damage to the bronchoscope. Some of the rigid scopes themselves have sharp edges that make it easy for the insertion tube of the flexible scope to be torn, and the option that the rigid scope offers of allowing the endoscopist another route of placing tools through the channel of the rigid scope alongside the flexible scope increases the risk of damage as there is limited space for all items to be passed.

Many of the larger training programs may have 50 combinations of different technologies available to them that have the potential of causing damage to the bronchoscope as well as the other tools used. This combination of technology to decide upon may make it difficult for one in training to become familiar with all aspects of a technology during their 1-year fellowship program. An example of this is illustrated as follows: A decision has been made to ablate an airway tumor with electrocautery. Many of these decisions are not made until the tumor is visualized in the airway at the time of the bronchoscopy because of the specific location of the tumor relative to an adjacent airway. So, even the type of ablation (electrocautery, laser therapy, or argon plasma coagulation) may not be fully decided upon until one does an inspection. Then one needs to decide upon the type of cautery tool to be used. There are snares, knifes, hot forceps, and blunt probes that can be used to accomplish the treatment (some with better results than others but dependent upon the comfort level of each operator). Once this decision is made, then the operator must take specific precautions to assure the safety of the patient and the equipment. Since this discussion has to do with the prevention of damage to the bronchoscope, we will not get into the safety aspects of the patient. The operator must be aware that the bronchoscope itself needs to be insulated if any form of electrocautery is to be applied, and even though this poses a more important risk to the patient, it is a potential cause for significant damage to the

Fig. 3.7 (**a**) Flexible bronchoscopy through rigid bronchoscope. (**b**) Accessory tools being passed through rigid bronchoscope

scope. There are safety markings on the cautery accessories to indicate that the device needs to extend at least this far past the distal end of the scope as to not pose a risk of electrical or heat damage to the scope. If this is not complicated enough while the operator is aiming the end of a device that may over the next few seconds cause significant bleeding in the airway and completely obstruct his view, we must remember that the interventional pulmonologist will probably be performing this risky procedure with the use of the rigid bronchoscope in the operating room. Now you have a situation where an electrocautery device has to be extended a specific distance from the distal end of the bronchoscope and the bronchoscope needs to be extended so that the barrel of the rigid bronchoscope is not near the line of fire of the cautery device. You may begin to see how damage can occur fairly easily.

Therefore, when budgeting for repairs in an interventional pulmonology program, one cannot compare it to the repair costs of a conventional bronchoscopy program or what has been spent on repairs in the gastroenterology department. This is a whole new challenge, and it is most important to review repair expenses closely from the beginning to gather a historical perspective of what true expenses will be. There is some literature published on the costs associated

with repairs for IP programs, but this can be difficult to interpret as there is tremendous variability as to what specific procedures are performed in each program. The differences between procedures being performed can have a huge impact on the relative risk of damage.

Proper Care of the Bronchoscope

As stated earlier, the investment put in to the care of this instrument can be the difference in fiscal success of any bronchoscopy program but is much more important in an interventional program as the risk of damage is that much greater. Today, the average bronchoscope costs more than $20,000 and some specialized scopes can cost twice that. Repairs to these instruments can easily exceed $100,000 per year depending on your practice. Fortunately, much of this damage is preventable, and it is critical to have a program in place that speaks to this issue. One of the best ways to prevent damage is to read and follow the instruction manual for each instrument.

To provide a systematic approach to the care of the bronchoscope, we can look at the different components of the procedure to best determine how the equipment should be handled. These components will be titled pre-procedure, intra-procedure and post-procedure.

Pre-procedure Care

A simple checklist to be reviewed before the procedure should include:

1. Transportation of the instrument to the procedure area: Transport the scope from the storage area to the bronchoscopy suite in something that will protect it from damage and dust (i.e., a plastic bin that is covered on the top).
2. A pre-procedure check of the systems.
   (a) Plumbing: Do the valves work and are channels clear?
   (b) Mechanical: Does the bending section flex the proper amount and in the right direction?
   (c) Electrical: Are all power systems functioning: processor, light source, and monitor?
   (d) Image: Do you get a crisp image with good color?
3. Proper preparation for the operator.
   (a) Proper lubrication of scope: Oil-based lubricants can degrade the rubber sheath; water-based lubricants are recommended.
   (b) Make sure that the cables coming from the processor to the scope are not twisted. The processor is intended to come from the left of the patient; otherwise, the cables will drape over the patient and put undue stress on the instrument.

Intra-procedure Care

Much of the care of the instrument that occurs during the procedure itself will be determined by the assistant, as the actual operator usually is concentrating on the navigation of the bronchoscope through the airways and may not be focusing on the surroundings that are taking place away from the video monitor.

1. Proper use of:
   (a) Bite blocks: Probably the single most costly "preventable" form of damage is from not using a bite block in patients that are thought to be adequately sedated. It is also important for the assistant to assure that the bite block is not misplaced during the procedure which may allow for bite damage from the patient.
   (b) Sedation (as above)
   (c) Accessories
      i. When placing accessories through the working channel, make sure that they are in the closed or "sheathed" position until they are visualized at the distal end.
      ii. If at any time visualization of the accessory is lost, immediately close or resheath the accessory and retract it into the working channel to prevent damage to the patient and/or the bronchoscope.
      iii. Never force an accessory through the working channel, or perforation of it can occur.
      iv. When retracting an accessory from the bronchoscope, always close or resheath the accessory.
      v. If the accessory device becomes stuck in the working channel, slowly remove the bronchoscope from the patient and then attempt to remove the device, keeping the angulation in the straight position.
2. Having an extra set of eyes.

As the operator has his or her eyes focused on the video monitor, it is easy to lose track of how the bronchoscope is being held or manipulated. The assistant needs to be cognizant of this and point out if the scope is being bent too acutely and suggest a correction.

Post-procedure Care

Much of the preventable damage that happens occurs from errors in the immediate post-procedural care of the scope. If there has been damage from bites or accessories that have caused a communication between the outer surfaces and the inner workings of the instrument, fluids can cause much more damage if allowed to leak inside. If this is suspected, then steps should be taken to eliminate this potential.

Fig. 3.8 (**a**) Leak tester. (**b**) Bronchoscope leak with bubbles after pressurization. (**c**) Bronchoscopy storage

Recommendations from the manufacturer should be utilized, including continuous pressurization of the scope during manual cleaning, drying the scope in a drying cabinet if available, and gas sterilization.

Normal steps to be taken after the procedure include:

1. Initial cleaning at bedside:
   (a) Wipe down insertion tube with wet gauze.
   (b) Flush water through scope with only the very tip submerged.
   (c) Suction air through for at least 10 s.
2. Transport to cleaning area in a leakproof container that is supported on the bottom (i.e., transport tray).
3. Leak testing (Fig. 3.8a):
   (a) Apply leak test before submersing fully in water to prevent fluid invasion,
   (b) Flex control lever for several seconds while under water to detect minute leaks (Fig. 3.8b).
   (c) Observe for sufficient period of time.
4. Proper disinfection, drying, and storage (Fig. 3.8c):

Follow manufacturer's recommendations for scope reprocessing.

Damage to the Bronchoscope

As carefully as the steps above are followed, from time to time, damage will occur to the bronchoscope. The manager responsible for overseeing the service should attempt to determine the cause of the damage. One should distinguish between damage that would be considered preventable in the hands of a careful operator versus damage that happens irrespective of the care that the operator takes in handling the equipment.

Preventable damage to the bronchoscope occurs when operators of the equipment or their assistants perform maneuvers that are not recommended with either the bronchoscope or its accessories. Simply put, if one follows the manufacturer's recommendations, essentially most of this damage would not happen.

Some examples of this type of damage include:

- Inadequate sedation of the patient resulting in bites in the instrument.
- The improper use of accessories damaging the working channel. When using devices like biopsy forceps, brushes,

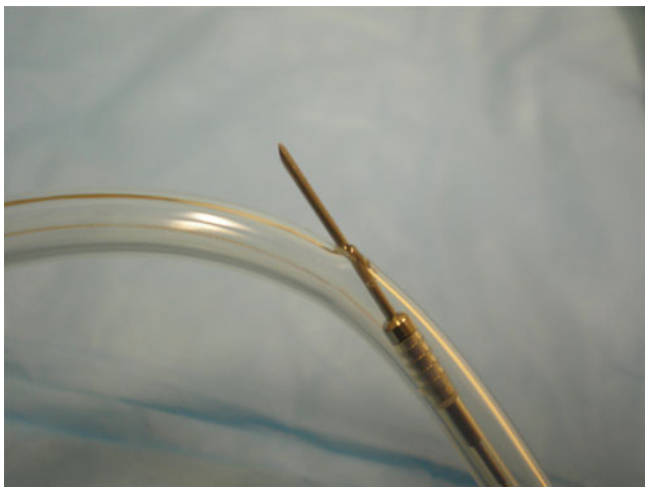

Fig. 3.9 Needle perforation through working channel of bronchoscope

or needles, care should be taken to insure that the sampling devices are not open during passage through the working channel of the instrument (Fig. 3.9). This is by far the most common reason for damage to the channel of the scope and is completely preventable.
- Improper transportation of the instrument leading to breakage.

Non-preventable damage is caused by the normal wear and tear of the instrument. Examples of this type of damage include:
- Leaks in the bending section without obvious trauma during a procedure.
- The degree of angulation of the bending section is not according to manufacturers specifications from stretching of cables which occurs over time.

Post-damage Considerations

In the unfortunate event of damage to the bronchoscope, there are many considerations to be addressed that may play into the determination of whether the scope should be repaired or not, and if so, how it should be repaired.

The decision to repair a scope, consider the purchase of a replacement scope, or not replace it at all can be based on some or all of these factors:
- Is the scope under a lease program or was it purchased outright?
- Type of damage (This will help indicate the cost of repair.)
- Age of scope
- History of repairs
- Is the scope under warranty? (It may not matter if it is from preventable damage.)
- Did this damage occur at a time in the fiscal year when requests for new scopes are to be submitted through capital request process?
- Is this type of scope one that you can live without (Is there an adequate number of similar scopes or could you use this money for a scope that better suits your practice?)
- What is the trade-in value of the damaged scope and how much will a new scope cost?

After you have this information, you can better make a determination as to whether or not to repair the instrument. At some point in the life of the scope, one needs to consider whether it is financially reasonable to repair it or whether it should be retired. This may be a scope whose useful life has expired a while ago, and you were hoping to just get another 6 months out of it before replacing it. If the decision is to retire the scope, there may still be some value in using it as a trade-in for a replacement. If the decision is to repair it, there are many options to consider. Some of them may be:
- Who do I have repair it? (manufacturer versus third party)
- What is the cost of the repair?
- What is the turnaround time for the repair? You may not be able to go without having this scope for very long.
- Are there loaner scopes available?
- What are the service warranties for the repair?

Prevention of Damage to the Bronchoscope

The first step to take in the prevention of future damage is to look historically at what types of damage have occurred in the past. Therefore, it is imperative to have a system in place that tracks the damage to the instrument with the type of procedure performed (including tracking those individuals performing the procedure). There needs to be a way to associate the scope used on a patient with the staff performing the procedure. (There are other infection control reasons to be able to track patients with the scope being used, but that does not pertain to this discussion.) A simple log book of repairs should be kept for each scope sent out for service. This will give you information so that when the scope is damaged in the future, then informed decisions can be made as to what the financial feasibility is for the repair.

When determinations have been made as to why damage has taken place, a plan should be developed to prevent future damage. This plan could be relatively simple, like protecting the scope from trauma during transportation, or could involve additional training of staff to make them aware of the idiosyncrasies of a particular accessory that tends to lead to damage.

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Bronchoscopy Unit Design for Advanced Procedures

4

Robert Garland

Introduction

Interventional pulmonology is a rapidly evolving field with new diagnostic and therapeutic technologies available. Advanced bronchoscopy unit design has become a topic of interest with the creation of many dedicated units around the world. No guidelines exist regarding optimal unit design, and when faced with planning such units, the "wheel" needs to be reinvented every time.

The challenges faced are to provide for current volume and types of procedures and to have flexibility in the design to accommodate for future growth. Specific area design must be considered as well as the flow throughout the unit.

Integration of the Procedure Unit with the Rest of Medical Center

Before embarking on the actual design of the physical space, one should consider very importantly where the unit will exist relative to other departments. By the nature of the acuity of patients served, there needs to be easy access to members of the code team, radiology, and even possibly surgery. Decisions should be made as to the types of procedures performed in this unit considering the safety of the patient. You may have tremendous plans for the grandest of procedure suites, but regulatory bodies in and outside the hospital may not deem it safe to perform these in this location. There exists the possibility that the more routine procedures are allowed to be performed initially and then more complicated ones added after safety measures are followed and the procedure unit has "proven itself" over time.

As important as where it will exist is how it will exist with other departments. This unit does not function as an independent space but relies upon the coordinated efforts of many departments throughout the hospital system. Consideration needs to be made of the following for the seamless transaction of the patient experience.

1. **Administrative Workflow**
   (a) Registration of patients
   (b) Obtaining medical records
   (c) Telephone communications between administrative offices scheduling procedures
   (d) Scheduling of patients via any software program used assuring it also gets on physician and unit schedules
   (e) Billing and required documentation submission
2. **Clinical Workflow**
   (a) Physical space issues between where patients may be seen in OP clinic and procedural unit
   (b) Waiting area for patient's family members; general waiting area used vs. a dedicated area for these patients
   (c) Use of transport system for the movement of inpatients to and from the procedural unit
   (d) Laboratory services including phlebotomy, IV
   (e) Radiology services
   (f) Anesthesia services
   (g) OR services should patient require this during a procedure

Philosophy of How This Procedural Space Functions

I am going to make the assumption that this space is strictly used as a procedural unit and any outpatient clinic visits will be conducted elsewhere.

Determining Procedural Volumes and Space Needs

To be able to determine the size of the procedure space required, you need to establish the number and type of

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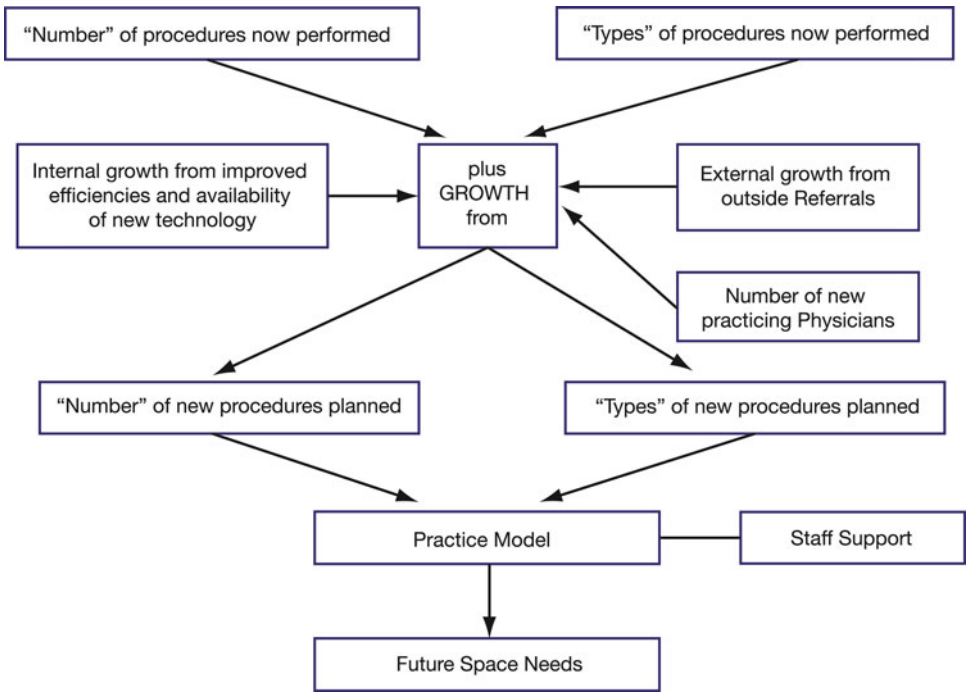

Fig. 4.1 Determining procedural unit space needs

procedures that will be performed over the useful life of the unit. In formulating a plan as to the procedures expected to be performed now and in the future, one must look at historical data to determine the types of interventional procedures and the volume to be expected going forward. Depending on whether this is an established practice and there is some history that can be drawn from, you may or may not have data to support the number and types of procedures as well as the staff support needed. It is much easier to justify your requests for new or additional space if you are able to show the administration 5 years of historical data with growth of revenue as opposed to the practitioner just starting a practice. In this case, you must rely on demographic information derived from hospitals databases regarding the disease populations that would lead to referrals, the referral patterns for surrounding practice groups, and the competition for patients in the population area.

As well as this information, it is necessary to project as accurate as possible the expectations to be accomplished over the next 5 years. These volumes will be the benchmark with which you will be measured.

Considerations need to be made of at least the following to allow for predictions as to the numbers and types of procedures before space requirements can be made:

1. The number of practicing physicians (now and in the future) and the practice model used to allow for optimal use of space, equipment, and staffing
2. Level of procedures to be performed:
   (a) Flexible bronchoscopy with some intervention
   (b) Rigid bronchoscopy
   (c) Medical thoracoscopy
   (d) Other chest procedures (thoracentesis, Chest ultrasonography, Pigtail drainage catheters, etc.)
3. What level of anesthesia will be administered (may be limited by hospital policy)
   (a) Topical anesthesia
   (b) Conscious sedation
   (c) Deep sedation
   (d) General anesthesia

Staff Support

It is equally important to the success of this procedural space to match the level of staff support required in the environment we are considering in this specialty.

Interventional pulmonology relies heavily on a variety of highly technical procedures and the associated equipment. New technology is developed at a very fast pace, and the staff needs to be able to operate and troubleshoot all modalities. This is especially true because physicians in this profession are operating on a compromised airway, and time can be critical should a piece of equipment malfunction. Depending upon the use of the unit, a decision needs to be made as to the utilization of a dedicated staff for IP procedures vs. endoscopy nurses cross-trained in advanced pulmonary procedures (Fig. 4.1).

General Requirements of Procedural Area

Hospital procedural suites must adhere to many regulatory bodies including but not limited to internal and external groups. An interventional pulmonology advanced procedure suite may be subject to the control of some of these:

1. ***Internal Regulatory Groups***
   (a) Life safety
   (b) Infection control
   (c) Radiation safety
   (d) Invasive procedures committee
2. ***External Regulatory Groups***
   (a) Department of Public Health (DPH)
   (b) The Joint Commission (TJC)
   (c) Centers for Medicare and Medicaid Services (CMS)

General Information that Should Be Available Regarding the Procedural Unit

Scope of services provided
List of physicians approved to perform specific procedures
Qualifications of staff support
Policy and procedures manual

Spaces Required for Procedural Unit Design

1. Reception
2. Preop and recovery
3. Procedure
4. Nursing workstation
5. Physician workstation
6. Storage
7. Reprocessing
8. Other?

Flow of Patients, Staff, and Equipment

Before we discuss the actual procedure spaces, we should consider the optimum flow through the unit for patients, staff, and equipment. In a perfect world, patients would experience their procedure by stopping at the reception area for a very short time, answering a couple of simple questions, and proceed to the procedure suite with no interruptions or delays and with no exposure to anything else going on in the unit that does not have to do with their own care. So, at least to address the last part, in a perfect world, we might have a procedural unit that has separate flows for the patient, staff, and equipment.

Patient flow may be designed to have patients begin their experience at the reception center and complete the required administrative duties, while family members are escorted to a nearby waiting area. From there, the patient is brought to the preoperative area in privacy through a corridor that is dedicated for patient transport only, unexposed to other patients or family sitting in waiting areas or equipment being rolled by the staff. Then, through the same hall to the procedure suite for their case and after, brought back to the recovery area in privacy to their bay to recover until it is time to be discharged. The patient is then reunited with family via this separate corridor to either the reception or waiting area.

Staff would use a more common hall to flow from their nursing station to the area that they are responsible for, whether to care for patients in the preop area, the procedure suite, or recovery. On this common side would also house the physician workroom and storage areas for nursing supplies and technical equipment. This hall would by its nature be much busier than the private hall used to escort patients. Nurses might be moving from one area to another and technical staff shuffling equipment and supplies to and from the storage, preop, recovery, procedure, and reprocessing areas (Fig. 4.2).

Realistically, space restrictions and funding may not allow this ideal flow to occur. Hopefully, there will be some middle ground that will be found to allow minimum exposure to the workings of the procedure unit for patients while providing the staff with the most efficient way to perform their roles. This means providing storage areas that are in proximity for nursing supplies to the areas that need them and other areas for storage of technical equipment that does not require movement over large distances.

Procedural Unit Requirements

1. ***Reception Area to Greet Patients***
   (a) Allows for administrative responsibilities to be completed/registration verified
   (b) Provides area where family members are directed toward waiting area
   (c) Space to direct inpatients to preop area (Fig. 4.3)
2. ***Preop and Recovery***
   (a) Number of beds required depends upon number and utility of procedural rooms.
   (b) Staff requirements depend upon above and practice model used (dedicated staff for this area vs. same staff used to prep/recover and assist in procedure).
   (c) Requires a private area for outpatients to change from street clothes to hospital garments.
   (d) Necessary equipment for area includes hemodynamic monitoring which should be flexible (modular) to adjust for acuity of patient served.

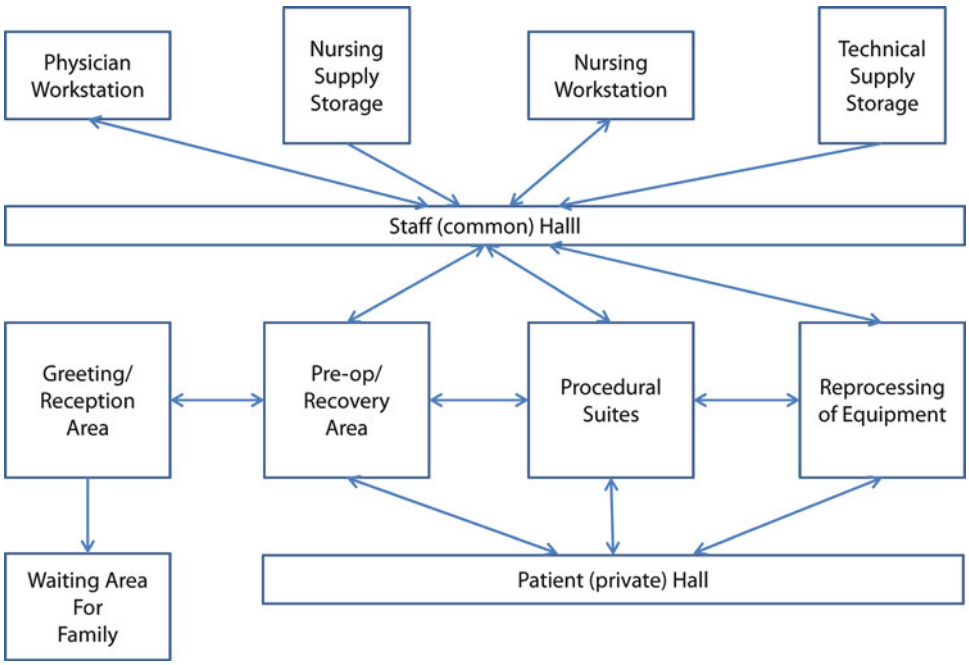

Fig. 4.2 Flow of patients, staff, and equipment

Fig. 4.3 Reception area

(e) Isolation room with negative airflow for potential of infectious airborne disease transmission.
(f) There are minimum standards for room sizes but must consider occasional equipment that may need to be placed there (x-ray, emergency equipment in event of cardiac arrest).
(g) Need to consider in the design the use of fixed walls for privacy vs. curtains which offer flexibility in their use. We have found that the combination of fixed walls on the side and a curtain across the front provides the advantages of both.
(h) Consider flexibility in cabinet design for the ease of restocking should product selection change over time. Also the use of portable storage carts for nursing supplies allows for carts to be replaced in there entirety and restocked at a location that does not interfere with patient care (Fig. 4.4).

3. ***Procedure Space***

Before design plans can be considered, one must decide upon how the room will function. For instance, the location of medical gas lines in the room cannot be determined until you know where the patient will be positioned in the room.

Fig. 4.4 (**a**) Nursing workstation centered around preop and recovery and (**b**) view of isolation room from nursing station

The architectural team cannot proceed with their drawings until the clinician makes this decision. You do not want to leave these decisions up to someone else and be left in a situation that you had control over but decided not to act upon. Too many times, a standard cookie-cutter model is selected, and the end users are left tripping over gas lines, extension cords, and video cables that were not placed in the best locations.

Therefore, the key to this space is the location of the patient bed with regard to movement into and out of the room; the flow of staff during the procedure as well as the required movement of equipment in and around the patient after patient is on the procedure bed.

Considering that there will probably be only one door used to move the patient to and from the room, then this area from the door to the procedure bed should be kept free of any permanent fixtures. I also think it is very helpful to be able to see the operator from the entrance to the room. This allows for easier communication and may allow for a sense of the progress of the procedure.

Given the above information, I believe it makes the most logical sense to locate the head of the bed toward the left hand wall as one would look into the room. Because bronchoscopy equipment connects to their processors and light sources on the left side, then any booms incorporated into the design to hold this hardware need to be positioned on this side of the patient. If the patients' location was reversed and the head was at the right hand with the feet facing the left as you looked into the room, then the boom used to house the processors and light sources would obstruct the entrance to the room, and visualization of the operator would be compromised.

If one wanted to locate the head of the patient at the rear wall with feet facing the entrance to the room, then the boom (or booms) for the video monitors would obstruct the view and may be a bit more obstructive moving the patient. We have found that locating the patients head toward the left hand wall works best for most of our applications. But equally important in the design is to have the flexibility to modify the locations of these booms for different applications. The logistical flow of staff positioning and the determination of equipment locations including booms all hinge upon how you decide to position the patient for their procedure.

Whether you have one procedure room or several, each must accommodate the needs of that particular patient at the time of that procedure as well as any equipment that could be anticipated, should any adverse event occur without having to scramble for equipment elsewhere in the unit. In a room that does complex airway cases, you must have the necessary backup supplies to support the maintenance of the airway should that be needed.

The size of the rooms must be large enough to accommodate the function of the room but not so large as to waste time getting supplies from a cabinet that is uncomfortably distanced on the other side of the room.

An early discussion needs to be made with the designers and the radiation safety office to determine if special considerations must be taken for the procedure space regarding the anticipated use now and in the future for radiology services. Some programs use fluoroscopy on a routine basis and depending on the use may require the procedure room to be isolated to protect those outside it from excessive radiation exposure.

There must be adequate counter space along the perimeter of the room for additional supplies that may be required during the procedure which should be readily available without having to hunt through cabinets. The counter space should include a designated area for specimen handling and enough space for computers needed for video documentation, PACS, or hospital information systems. We have found that there generally needs to be some form of system for image capture directly at the bedside even if the majority of video documentation is planned in the physician workstation.

As mentioned, there should be consideration as to the location of medical gases and vacuum to accommodate the movement of staff and patients.

Considering the trend in endoscopy suite design for ease of use, flexibility, and infection control advantages, the use of equipment booms, which removes any equipment contact from the floor, has become more and more popular in procedure suites outside of the operating room environment. Generally, there is one equipment boom to house the larger stationary hardware that will be used during most cases in that room and one or two additional booms to support the video monitors needed for a variety of positioning during different procedures. These equipment booms do not come cheap and may cost well over $100,000 but are worth every dollar spent on them. A central switching system can be integrated into the room at an additional cost which will allow for different devices to be imported to the selected video monitor outputs without having to hardwire these separately for each case.

The total number of video monitors available should be sufficient for all endoscopic views as well as radiology images required during a particular case and should be able to be visualized by both the operator and assistant without having to turn their heads from the position they are in during the procedure. This may include several images including endoscopic, ultrasound, and CT scan which may be needed simultaneously. Our own personal experience has taught us that trying to determine the number of monitors required by viewing some cut sheets left us short of what we truly needed.

After considering every situation that we could think of to determine an adequate number of monitors (and the procedure rooms were functional), not only then did we realize that the assistant did not have an endoscopic view unless that person rotated their head 90 ° to the right. This required that person to take their eyes off the tool they were using to see the accessory on the screen. Consequently, an additional monitor was installed for the assistant (who is normally positioned looking at the bronchoscopy operator). This monitor was located on the equipment boom to the left of the operator directly in line with the assistants view. I would suggest that those responsible for the decisions on the room design actually gather the staff in a role-playing scenario to best determine the location of the patient, equipment, and monitors for optimum function (Fig. 4.5).

Whether one chooses to use an operating room table or stretcher depends upon the procedure planned and what you are comfortable with. There are advantages to each but expect to pay $30,000 for a fully equipped electric OR table compared to around $1,000 for a stretcher.

Adequate and flexible storage should be a priority demanded in each procedure room. Designers seem to leave this as an afterthought, and the end users are left with a lot of extra supplies that have no place to call home and usually are then placed in some corner away from the procedure room until they are desperately needed during a case. Then the scramble is on to remember where they were put.

Whatever the room is designed to be used for should have ample supplies in the room. I would consider the use of wall-mounted storage cabinets. They are very flexible, and you can easily change the shelving bins to accommodate supplies whose dimensions change over time. Some of the newer ones

Fig. 4.5 Procedural suite

Fig. 4.6 Storage cabinets

are mounted on a rail system and can be moved along the wall for flexibility should the room design needs change and also are off the floor for infection control advantages (Fig. 4.6).

There also needs to be a sufficient number of procedure tables for each procedure room. I would suggest at least two and they should be on wheels to allow for movement in close enough to the procedure area with enough surface area to prevent any supplies from being too crowded or falling off the table (the primary table should be at least 5 ft by 3 ft).

In anticipation of the need for multiple size or style bronchoscopes during a single procedure, there should be communication in advance of the procedure from the staff attending or fellow as to the potential need for such. That way, support staff is not put in the awkward position of having to leave the procedure room to search for the required additional scope. Also, if it was reserved for this case, there would not likely be the chance that it was being used for another case during the same time.

Fig. 4.7 Bronchoscopy inventory

On the topic of bronchoscopes, we must consider what the correct inventory should be for the entire interventional pulmonology program. The proper number and types of bronchoscopes on hand are crucial to the success of an IP program. Many factors will determine the necessary inventory to avoid shortages which affect productivity. Some of these factors include:

(a) The number of practicing physicians
(b) The practice model which will determine how many physicians will be performing procedures at the same time
(c) Whether other services in the hospital system have access to the same bronchoscopes
(d) How scopes are reprocessed (where and how this is done determines turnover time)
(e) The types of scopes used (diagnostic, therapeutic, ultrasound, pediatric, ultrathin) and more importantly, the combination of multiple scopes that may be used during the same procedure
(f) The current age of the scopes in service and useful life expectancy (Fig. 4.7)

4. ***Nursing Workstation***

This central workstation would be located along the common hall where staff would use this space as a command post to monitor patient status, write notes, and communicate with physicians and other staff. Here will reside hemodynamic data for all patients along with that available at the individual bedside. It would be centrally located in such a way as to visualize all patients in the preop and recovery areas, since this is the primary focus. Separate nursing staff and physicians monitor the status of patients while undergoing procedures in the actual procedure rooms. A call system from patient's bedside would alarm in this area along with visual cues outside of each patients bay. This workstation is physically located close enough to the procedure rooms as well to offer assistance should the need arise.

5. ***Physician Workstation***

This private space for physician staff (also positioned on the common hall) allows an area for them to congregate between procedures for dictation of notes, access to viewing and printing reports, and for discussion with other physicians.

This form of a command center also allows communication throughout the unit with two-way audio and video feeds to the actual procedure rooms. For the purpose of visualizing procedures in other areas, the communication system here can direct the cameras in the procedure rooms to other conference rooms in the hospital system and through its own video conferencing system to anywhere there is a system at the other end. In this space, any video documentation can be edited and finalized before attaching to the final reports.

For many years, still images were the only options available but in recent years, the quality of video clips have improved tremendously and are in formats that are easy for the endoscopist to share with referring physicians.

While there are many stand-alone systems available for capturing video and stills from the procedure as well as proprietary systems to record the procedure notes, the challenge still lies in finding a system that can integrate all of these needs into a seamless program together. As advanced as our

Fig. 4.8 Physician workstation

program is, in order to get the highest quality for our images, we have to rely on different systems to import these images into our dictation system (Fig. 4.8).

6. ***Storage***

Over the past several years, it has become more obvious that space in medical centers is at a premium with the need to keep inventories at the leanest margins possible; consequently, every effort must be made to conserve expenses by anticipating use of accessories and supplies. Hospital purchasing and budget departments can provide records on past expenses to gage what anticipated needs may be, moving forward.

With this in mind, I would envision having two main storage areas along the common hall with efficiencies of staff and conservation of supplies in mind. One would contain nursing and general medical supplies in an area of close proximity to the preop, recovery, and procedure suite, while the other would be used for storage of technical equipment and be located close to the procedure suites and reprocessing area. The storage of supplies would utilize par level stocking which through distribution services will provide the least amount of inventory required based on prior usage and will assure rotation of inventory to minimize the risk of using expired supplies. Both will also offer the most efficient use of staff time by minimizing the distance and time required to travel to these areas for replacement supplies or equipment.

7. ***Reprocessing***

There are no specific standards related to bronchoscopy reprocessing. All recommendations come from our peers in the GI profession and specific hospitals' infection control departments. But as much as it is similar, the equipment is different in many ways, and I believe that there needs to be similar standards for infection control issues related to proper handling of bronchoscopy equipment. Bronchoscopes are generally smaller in size and have consequently smaller diameter working channels which may make cleaning potentially more difficult. One upside is that most bronchoscopes utilize single-use disposable suction and biopsy valves which have the advantage over reprocessing the valves used in GI which mainly use reusable valves.

Consequently, we are left with figuring out for our own patients what is the best way to properly care for them in terms of preventing cross infection between patients as well as contamination of the equipment after proper reprocessing.

A separate discussion on infection control with regard to transport of soiled and clean bronchoscopes should be considered. We need to determine how to best move the instruments that have been reprocessed from their storage area to the procedure room thereby protecting the patient from contamination from the environment and soiled surfaces and also protect the health-care practitioners from diseases related to a contaminated bronchoscope during the postprocedure period until the scope is moved to the reprocessing area.

There are many solutions to these issues, but one that seems relatively simple is a system we have incorporated into our practice which uses a tray or plastic bin that has sterile liners used to carry scopes from the clean storage area to procedure rooms. A cover, which is labeled as "clean," is placed over the top during its trip to the procedure room, and after the procedure, the scope is placed in the same tray and the cover is replaced with another provided that is labeled "contaminated." This should eliminate any confusion as to whether a scope has been used or not.

There are separate infection control steps that should be taken at the end of the procedure to initially clean the scope at the bedside to decrease its bioburden which are out of the

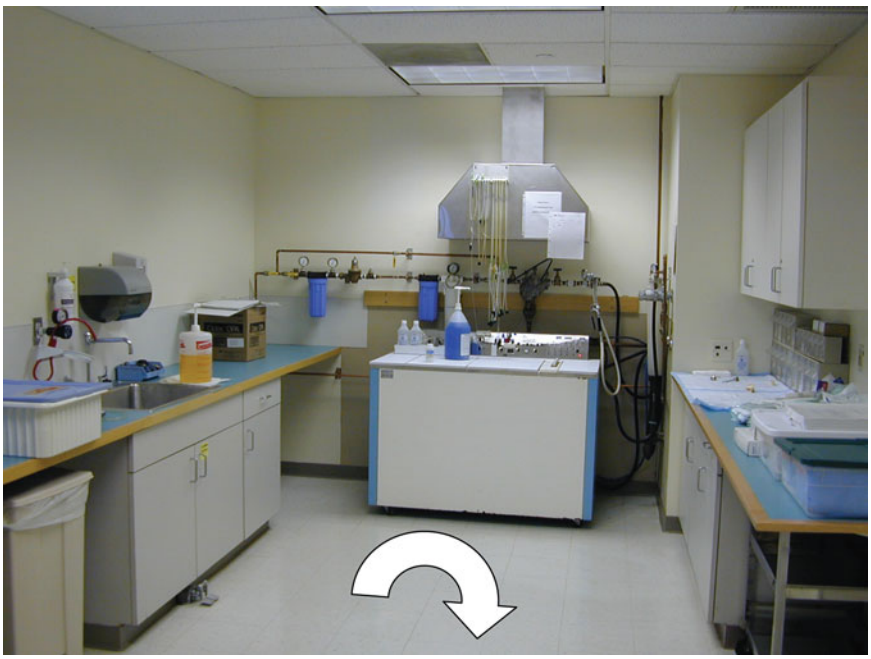

Fig. 4.9 Reprocessing area with directional flow

context of this publication but should be part of any hospital's infection control policies on endoscopy-related procedures.

There should be segregated areas in the reprocessing suite specifically for precleaning, reprocessing, reassembly, and clean storage and should flow in a circular fashion to prevent any crossover of soiled equipment into clean area and vice versa (Fig. 4.9).

Ideally, the reprocessing area should be in close proximity to the procedure suites for ease of transport and to prevent the instruments from having to sit for periods of time and allowed to dry out and make the reprocessing more difficult.

An additional step in the prevention of the development of bacteria in the reprocessed scope is the proper drying of the scope. Standard recommendations suggest the use of a postreprocessing alcohol flush to allow for better evaporation of the working channels. One additional method of drying the working channels that has been recommended is to place the scope in a drying cabinet which uses a desiccant to remove moisture from the air that is pumped through the internal channels of the scope.

8. ***Other Spaces?***

You may want to consider an additional space in the procedure suite that would be dedicated for the training of junior staff and an area that could be used for what we like to consider "technology development." It is very helpful to have a space which is in the suite itself where hands-on training can take place immediately prior to or even after a procedure to demonstrate a technique to better utilize ones skills. We have found in the past that if this space is located outside the suite itself, it tends to not be used because of time and distance limitations.

As the development of technologies continue evolving at such a rapid pace, we find more and more equipment being trialed with the need for reviews on a regular basis. This space is perfect for this purpose as it does not hamper the flow of patient care since it is not in the procedure room itself and staff are not felt rushed to learn while the room is being turned over for the next case (Fig. 4.10).

Additional Equipment Needs and Spaces to Be Considered for Procedure Unit

(a) Emergency equipment – code cart with portable oxygen and portable vacuum for transport of patients.
(b) A secure area for medications with refrigerator if needed.
(c) Shut off for medical gases used in the adjacent area.
(d) Negative airflow system for specific rooms in preop, recovery, and procedure suite.
(e) An area immediately outside procedure rooms for storage of personal protective equipment and inside for disposal of such as well as sink.
(f) An area set aside for the storage of specimens prior to transport to their respective labs. The initial prep should take place at the bedside to prevent mislabeling of specimens with other patients. There also should be a location used to hold specimens which can be used to log them out.

Fig. 4.10 Training/technology development space

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Quality Control Mechanism for Endoscopic Procedures

5

Michael J. Simoff

Introduction

The desire for quality health care continues to create national headlines. Whether it is people in search of the best doctor for their problem, the *100,000 Lives Campaign* created by the Institute for Healthcare Improvement or the Centers for Medicaid and Medicare Services' (CMS) Hospital Value-based Purchasing Program designed to pay hospitals that meet set performance standards for various quality measures, quality control, and quality assessment has become commonplace terms in both medical journals and the lay press.

Most physicians and other individuals running programs, such as bronchoscopy/endoscopy suites, have had little formal training in the practice of quality control and quality assessment. Despite this lack of experience, the social and financial climate of the practice of modern medical management continues to expect appropriate use of quality control and quality assessment measures. Quality data is being collected by numerous agencies and businesses and is being used as part of institutional reporting on capabilities of diagnostic yields of testing, outcomes of procedures, advertising low risks of complications, as well as a host of other facts. It is data like this, which will affect the potential "pay for performance" principles that are beginning to evolve in the insurance industry. Similarly, quality issues will affect the accreditation of trainees and privileges for physicians to perform procedures in the future.

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Quality Improvement

Quality improvement refers to the methods of improving processes of clinical care. Quality improvement often evaluates more than a single simple problem; it is often used to look at the operation of entire systems. A system, as a quality term, identifies bundles of related clinical processes. Therefore, system improvements are methods of quality improvement of these bundles of clinical activity (i.e., ventilator bundles in the intensive care unit, final time-outs before procedures, or patient management protocols). Much of evidence-based medicine is built around the concept of systems improvement.

As an example of the acceptance of quality control and improvement measures, the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Internal Medicine (ABIM) both acknowledge the importance of quality improvement. In 1999, the ACGME adopted a set of six clinical competencies as the goals of graduate medical education. One of the competencies identified is "practiced-based learning and improvement." This competency includes skill in practicing evidence-based medicine and the ability to "systematically analyze practice using quality improvement methods, and implement changes with the goal of practice improvement." The routine use of quality improvement should be the goal of any bronchoscopy program. Improvement upon how medicine is practiced and procedures performed is the only way to develop and maintain clinical superiority. Trainees will learn this much more completely as they see it integrated into the daily practice of medicine.

Quality Control

Quality control is the use of operational techniques and activities employed to ensure that a certain level of quality for a product or service is accomplished, which adheres to a

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defined set of quality criteria or to meet requirements that are established. Quality control may include whatever action is deemed necessary to provide for the control and verification of certain characteristics of a product or service. The basic goal of quality control is to ensure that the products, services, or processes provided meet specific requirements and are dependable, satisfactory, and fiscally sound. In order to implement an effective quality control program, a program must first decide which specific standards the product or service must meet.

Essentially, quality control involves examination of the product, service, or process for certain minimal levels of quality. The subsequent goal of a quality team is to identify products or services that do not meet the specific standards of quality established at their institution and employ quality control methodologies to evaluate and ultimately correct the problem.

This is very well exemplified by the events, which received considerable media attention in 2002 at Johns Hopkins Medical Center, where two patients died of complications of pneumonia after having undergone bronchoscopies. The problem of increased number of pseudomonas infections was not unique to Johns Hopkins. It was at Skyline Hospital in Nashville, Tennessee, that a team of healthcare professionals who had also identified an increased number of pulmonary patients contracting pseudomonas infections that the problem was recognized. Their quality assurance team reviewed and analyzed all available data and identified the problem causing this increase in infections was a design flaw in the biopsy port of a bronchoscope. The institution took this to the manufacturer, and the Food and Drug Administration, beginning the nationwide correction of a problem, which could have caused even more deaths if left unrecognized.

Quality control is a method by which a review of all factors involved in a process or production is evaluated. This includes:

1. Hard elements: the identifiable parts of a process: controls, equipment, job management, individual or team performance, integrity criteria of the process, as well as appropriate records, images, and data that were recorded
2. Competence: including knowledge, skills, experience, and qualifications
3. Soft elements: less measurable variables such as personnel integrity, confidence, organizational culture, motivation, team spirit, and the integration of quality measures into the culture of a practice

In order to implement an effective quality control program, the following must be established:

1. Decide which standard is to be met.
2. Evaluate the extent of quality control testing (i.e., how many are to be tested).
3. Determine what data is to be collected.
4. Corrective action is then decided upon and taken.
5. Quality control processes must be then become ongoing.

Quality control systems mandate that periodic random inspection of the product or process be performed. One of the most basic quality control techniques is to inspect the results of the production or service delivery process to ensure that it conforms to requirements established. In bronchoscopy, this suggests that complication rates, diagnostic test yields, equipment calibration, and morbidity and mortality need to be reviewed and analyzed as part of the operation of the unit.

As stated by Morris A. Cohen, Wharton professor and Codirector, Fishman-Davidson Center for Service and Operations Management, "you can't manage what you can't measure" is especially true in quality control. Collecting data routinely is paramount to establishing quality control programs. Another business adage is the 80/20 rule, "80% of the problems are caused by 20% of what you do." More basically than a good measurement system understands what needs to be measured. This fine tuning of data collection will guide the overall direction of a quality control program.

Quality Assurance

Quality assurance is a system for evaluating performance, by using systematic monitoring and evaluation of various aspects of a project, service, or facility, such as a bronchoscopy suite. It is used to maximize the probability that minimum standards of quality are being attained by all operational processes. Quality assurance includes all activities implemented to provide adequate confidence that a process or system will fulfill the requirements for quality (Figs. 5.1 and 5.2). In most bronchoscopy suites, quality control, quality assurance process can be merged to create quality improvement projects.

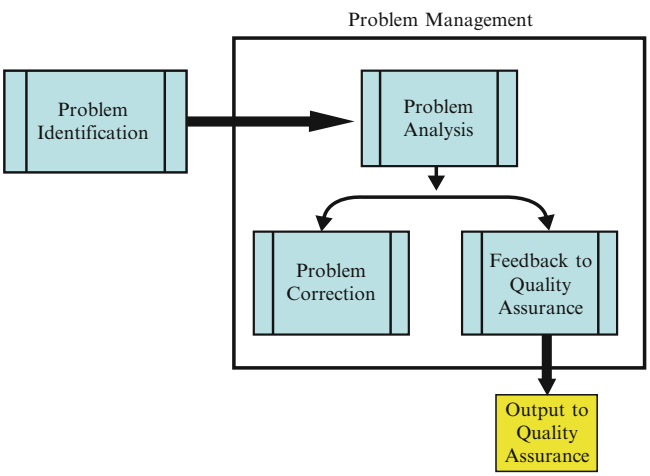


Fig. 5.1 Typical quality control steps

Methods of Quality Improvement

Developing a quality monitoring process requires the use of an established system. This system can be as simple as those outlined in Figs. 5.1 and 5.2 to processes that require advanced instruction. There exist numerous monitoring methods to facilitate consistency and standardization in performing monitoring. Next, several well-established methods of quality improvement will be discussed. Many of these systems have similarities, but the overall implementation must be user friendly to the team using these tools.

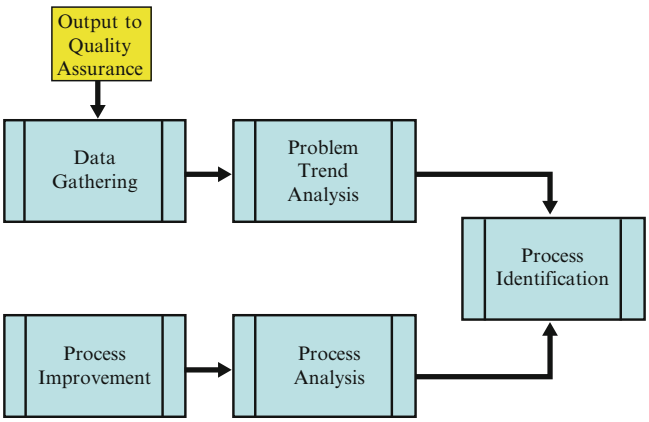


Fig. 5.2 Typical quality assurance steps

The FADE Model

The FADE model was developed by Organizational Dynamic Institute of Wakefield, Massachusetts. There are five steps in using this model for a quality improvement project (Fig. 5.3):

1. *Focus*: A process or problem to be improved must be clearly defined at the outset.
2. *Analyze*: Data must collected and analyzed to establish a baseline. From this analysis, the goal is to identify the root causes of the problem being studied.
3. *Develop*: Based upon the data analysis, possible solutions are evaluated and an action plan for improvement is created. This should include components of implementation, communication, and the system of measuring and monitoring to be used after the program has been put in place.
4. *Execute*: The process that has been developed is now put into effect. If this is a large-scale program, for instance, at an institutional level, pilot programs should be considered to test the process and monitoring systems developed.
5. *Evaluate:* It is also at this step that reevaluation of the original goals of the project is reviewed and any modifications of the program developed or variables measured are to be corrected. Once the process of improvement has begun, an ongoing monitoring process must remain in place to maximize the effects of the quality insurance program instituted and ensure its long-term success.

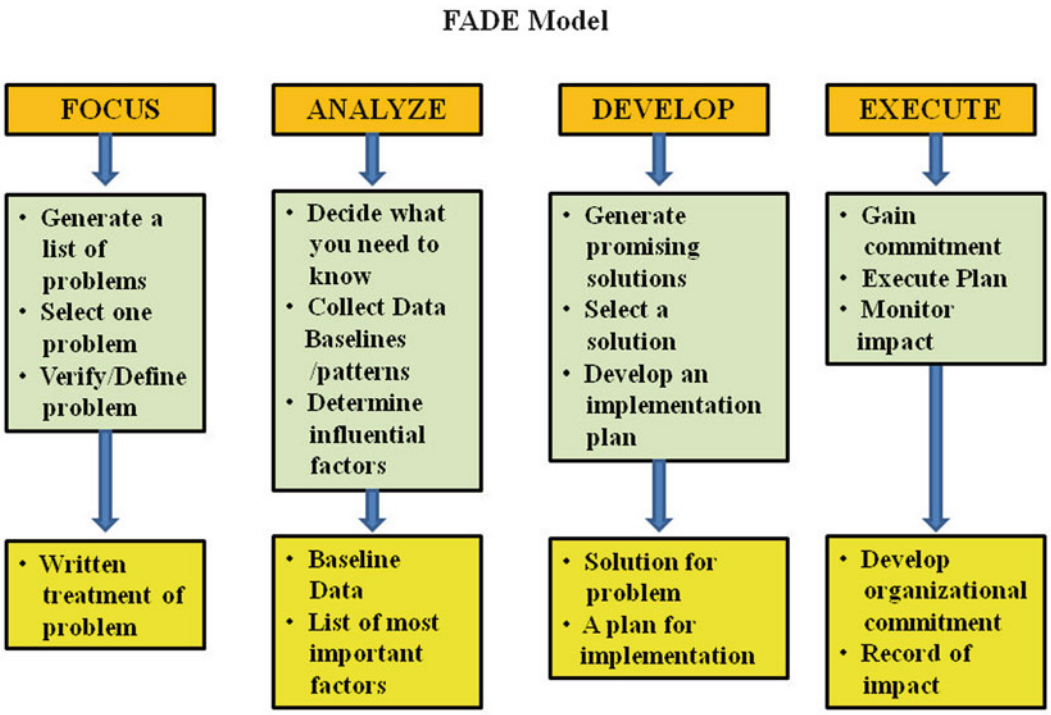


Fig. 5.3 FADE

PDSA

Another commonly used quality improvement technique is the PDSA cycle:

1. *Plan*: An initial idea or issue for change must be formally identified. Contributions from members of the team involved or a quality committee can be used to fully define the proposal.
2. *Do*: The plans that develop in number 1 must be carried out according to the parameters set.
3. *Study*: The results that are created by implementing the plan are then evaluated.
4. *Act*: After the results have been adequately analyzed, a plan of action must be developed to improve the quality program developed.

After the action has taken place, a new plan is formulated, and the process is repeated until the desired goal is achieved.

Six Sigma

Six sigma is a much more comprehensive program than can be effectively taught by a single chapter. Six sigma originates from a statistical modeling technique for manufacturing processes. A six sigma process is one in which 00.00066% of the products manufactured are expected to be free of defects (3.4 defects per million units). Six sigma is a name coined by Motorola, USA, in 1986, to identify a business management strategy they had developed. Six sigma has evolved over time as a method to improve the quality of process outputs by identifying and removing the causes of defects or errors in a process. Six sigma techniques also help to minimize variability in manufacturing, business, or other processes. Much of the new LEAN techniques of quality control being taught at health care systems is based on the six sigma philosophy.

The two major techniques used as part of six sigma:

1. *DMAIC*: This is used for projects designed to improve existing processes. This project methodology has five phases:
   (a) *D*efine the problem.
   (b) Measure and collect relevant data.
   (c) Analyze the data collected and identify a cause-and-effect relationship.
   (d) Improve the current process.
   (e) Control the process to ensure that any deviations from the new targets are identified quickly. This step also requires implementing systems of ongoing measurement.
2. *DMADV or DFSS*: These systems are used for projects developed to create new products or processes, such as adding a new procedure to the bronchoscopy section.
   (a) *D*efine the problem.
   (b) Measure and collect relevant data.
   (c) *A*nalyze the data collected and identify a cause-and-effect relationship.
   (d) Design the details needed for the new product/process. In more advanced systems, this could require simulations or modeling.
   (e) Verify that the design will work. Plan and execute a pilot run to identify any potential mistakes in the process.

Other

The goal of quality improvement can be attained using less sophisticated tools for analysis than the FADE, PDSA cycle, or Six Sigma:

1. *Flow charting process*: Flow charting can be used to assess a process within the bronchoscopy suite itself. This technique can identify process issues at any level throughout patient or instrument throughput. Bottlenecks of flow are usually identified, allowing program improvement with correction of these areas of concern.
2. *Self-reporting of critical incidents*: In many ways, this is what morbidity and mortality evaluations should be. If the review of these events does not involve identification of system or personnel problems, it has not been effective as a quality improvement tool.
3. *Database development*: Using a database that prospectively collects information allows evaluation of problems which may arise, in a more dynamic fashion that having to return to retrospective data review on every occasion. Databases can be used at institutional levels, system levels, or nationally as is seen with large registries (i.e., patient registry for primary pulmonary hypertension, Pennsylvania Idiopathic Pulmonary Fibrosis State Registry, etc.).

Quality Control Measures for Endoscopic Procedures

Areas of potential quality control intervention have been divided into:

1. Procedural processes
2. Equipment use in procedures
3. Other

These topics are only a basic outline for potential areas of quality control projects. The examples given are exactly that examples given to help illustrate problems encountered with solutions.

Procedural Processes

Procedural processes can be influenced by the practice at individual institutions. If bronchoscopy is performed in a bronchoscopy suite vs. an endoscopy area vs. an operating room, there are different administrative and leadership issues,

which can affect the overall procedural processes of bronchoscopy. Procedural processes include the standardized performance of procedures, patient management protocols, complication rates, equipment failures, diagnostic yields, and registries.

A. Performing Procedures

At most institutions, there are multiple bronchoscopists working with multiple fellows, nurses, respiratory therapists, and other personnel in the performance of bronchoscopies. If every combination of personnel is using individual preferences in the performance of their portion of the bronchoscopy, there would be very poor efficiency for the entire team. Efficiencies can affect not only the yields of procedures but the time needed to perform the procedure, the time necessary to set up or break down the room, risk the proper processing of the specimens, and increase the risk to patients as well as equipment.

Performing procedures can be broken down into functional components that quality control issues can more specifically address.

1. Procedural Setup
   (a) *Focus*: To standardize the setup of the therapeutic table in the operating room. Multiple nurses and technicians were occasionally required to set up the room, particularly on off hour cases. Many instances of not having the correct equipment on the table or not being able to identify the location of some equipment on the table occurred.
   (b) *Analyze*: Notes were made on the various setups and physician variances.
   (c) *Develop*: All physicians, nurses, and technicians agreed on what equipment was necessary for the table and how it would be positioned.
   (d) *Execute*: Pictures of the "accepted" table setup were taken. Inservices were completed for all personnel. Photos are left in the operating room for any personnel to refresh their memory about room requirements.
   (e) *Evaluate*: The program still exists. The photos remain in the operating room easily available for review, and inservices are held for all new personnel on a biyearly basis. The setup time has been reduced by the repetition of setting up the same table. The process had additionally selected all ancillary supplies to be used with each case. These supplies are now stored in the operating room to make them easily available for initial setup and/or replacement during the procedure, and during procedures, all physicians and supporting staff have been informed where each piece of equipment is located (Fig. 5.4).
2. Medication monitoring
   New medications and various recommendations are continuously changed and modified for the use of medications. Combinations of narcotics, benzodiazepines, hypnotics, and inhalational agents can be used for sedation during bronchoscopy. It is necessary to choose effective combinations of medications to be used for moderate, deep, or general anesthesia:
   (a) Use of medications should be standardized within the bronchoscopy suite. This will ensure expected responses and results to the medications, allowing the appropriate reversal agents to be readily available.
   (b) When the medications are chosen, appropriate compliance review data must be collected. These data sheets are collected and analyzed comparing data to medication use (Fig. 5.5).
3. Procedural Standardization and Patient Management Protocols
   (a) Personnel should all be practicing using similar procedural protocols. If there are significant outliers to the performance of procedures, then any variances in morbidity, mortality, or diagnostic yield cannot be easily assessed:
      i. The number of transbronchial biopsies that should be routinely performed for the bronchoscopic assessment of a mass or solitary pulmonary nodule
      ii. The amount of fluid instilled and the amount expected on return to perform a bronchoalveolar lavage (BAL)
      iii. Appropriate mediastinal staging with EBUS TBNA following lymphatic drainage maps of lobar lymphatic flow
      iv. Establishing the appropriate management protocols, for example:
         1. Complex tracheal stenosis
         2. Endobronchial carcinoid tumors treatment and follow-up
         3. The evaluation and diagnosis of lymphoma

   The list for this section could continue to the end of this chapter. It is important that program directors identify those clinical circumstances that are most relevant addressing common clinical problems to individual programs and provide appropriate leadership in these areas. Having all protocols at a readily available location to physicians and bronchoscopy personnel is imperative to its functional success (Fig. 5.6).
4. Pathologic Sample Handling and Management
   It is often assumed that diagnostic yield is the result of procedural expertise. Unfortunately, this is only part of the issue. Pathologic specimen processing, whether it be slide preparation, sample handling, or labeling, can potentially negatively affect the diagnostic result of a procedure.

As an example, a new nurse was hired to the bronchoscopy suite. She had previously worked at another institution in the endoscopy area and was "trained." As part of our

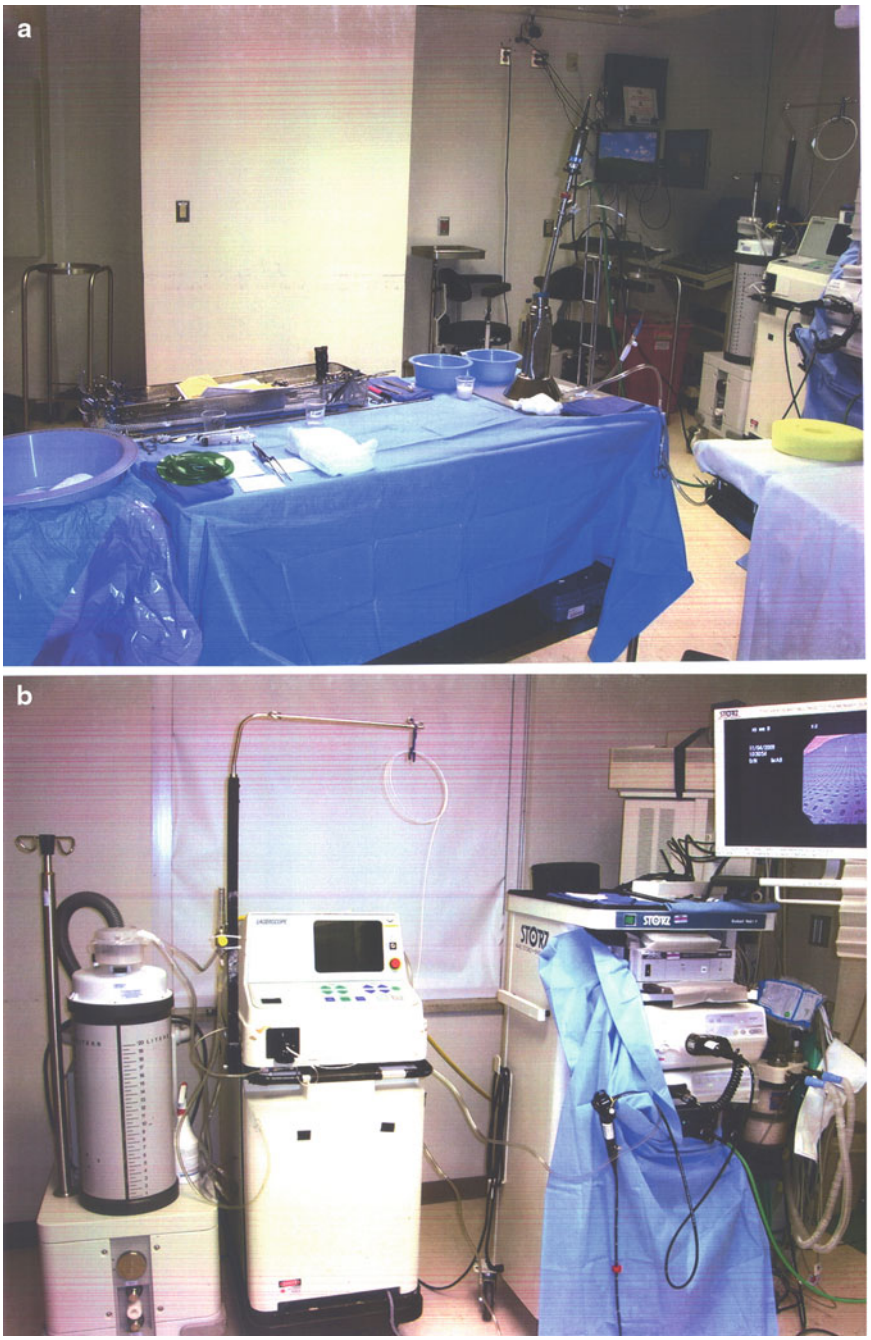
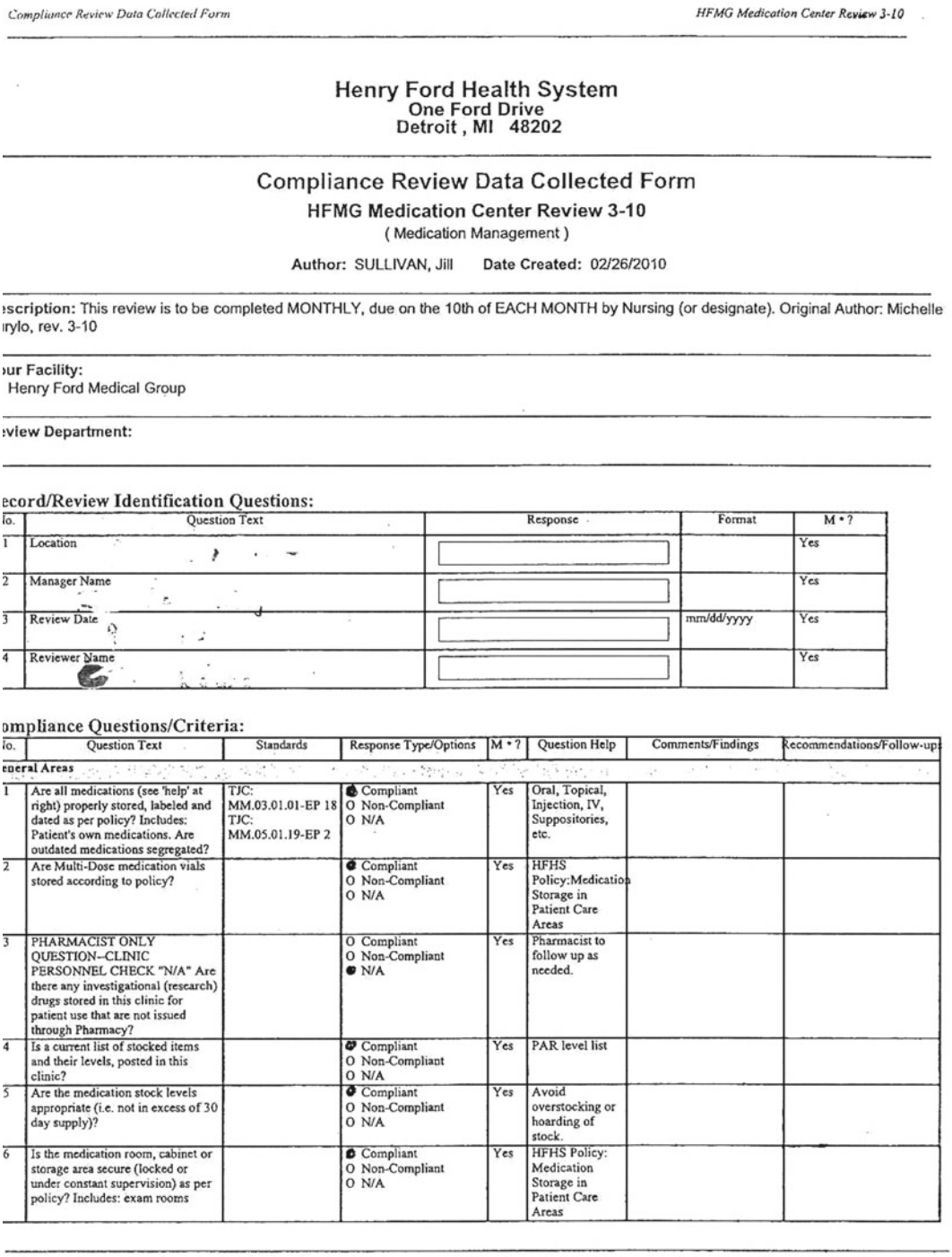


Fig. 5.4 (**a**) Table setup; (**b**) Room setup

continuous quality control projects, it was noted several months later that yields on cytologic brushing had diminished. The problem was *focused* on and specific data was collected and *analyzed*. It was then identified that all physicians were having reduced yields, not only one or two. It was eventually recognized that the days that the new nurse was assisting in the bronchoscopy suite were days which had zero yield on cytologic handling. A plan was *developed* and *executed*. All nurses and physicians were given didactic training on handling of all pathologic specimens that could be collected during bronchoscopy. This was followed by hands-on training with a pathology technician and a staff pathologist for all personnel. The results of bronchoscopy were then *evaluated,* and it was identified that yields were better than six months previous to the quality control intervention. It was determined that pathologic specimen training would be required for all new personnel to be signed off on as part of their orientation training period.

Other examples of pathologic specimen handling quality control programs include:



Compliance Review Data Collected Form *HFMG Medication Center Review 3-10*

Henry Ford Health System
One Ford Drive
Detroit , MI 48202

Compliance Review Data Collected Form

HFMG Medication Center Review 3-10

(Medication Management)

Author: SULLIVAN, Jill **Date Created:** 02/26/2010

escription: This review is to be completed MONTHLY, due on the 10th of EACH MONTH by Nursing (or designate). Original Author: Michelle irylo, rev. 3-10

our Facility:
Henry Ford Medical Group

eview Department:

ecord/Review Identification Questions:

lo.	Question Text	Response	Format	M * ?
1	Location			Yes
2	Manager Name			Yes
3	Review Date		mm/dd/yyyy	Yes
4	Reviewer Name			Yes

ompliance Questions/Criteria:

lo.	Question Text	Standards	Response Type/Options	M * ?	Question Help	Comments/Findings	Recommendations/Follow-ups
eneral Areas							
1	Are all medications (see 'help' at right) properly stored, labeled and dated as per policy? Includes: Patient's own medications. Are outdated medications segregated?	TJC: MM.03.01.01-EP 18 TJC: MM.05.01.19-EP 2	● Compliant O Non-Compliant O N/A	Yes	Oral, Topical, Injection, IV, Suppositories, etc.		
2	Are Multi-Dose medication vials stored according to policy?		● Compliant O Non-Compliant O N/A	Yes	HFHS Policy:Medication Storage in Patient Care Areas		
3	PHARMACIST ONLY QUESTION--CLINIC PERSONNEL CHECK "N/A" Are there any investigational (research) drugs stored in this clinic for patient use that are not issued through Pharmacy?		O Compliant O Non-Compliant ● N/A	Yes	Pharmacist to follow up as needed.		
4	Is a current list of stocked items and their levels, posted in this clinic?		● Compliant O Non-Compliant O N/A	Yes	PAR level list		
5	Are the medication stock levels appropriate (i.e. not in excess of 30 day supply)?		● Compliant O Non-Compliant O N/A	Yes	Avoid overstocking or hoarding of stock.		
6	Is the medication room, cabinet or storage area secure (locked or under constant supervision) as per policy? Includes: exam rooms		● Compliant O Non-Compliant O N/A	Yes	HFHS Policy: Medication Storage in Patient Care Areas		

Fig. 5.5 Compliance review data collected form

(a) Labeling of specimens: Specimens were previously sent out of the bronchoscopy suite unlabelled leading to confusion on whose specimen it was. Solution developed: Labeling should be done at the location that the procedure is being performed (Fig. 5.7).
(b) Checking specimens: Specimens were sent down to pathology with incorrect or incomplete testing identified. Solution developed: A staff physician must now review all specimens with paperwork prior to sending it to pathology (Fig. 5.8).
(c) Logbook: A logbook was developed to manage all specimens sent out. The results are compared to specimens that had been sent out to ensure all results are available. After checking in specimens, the physician must sign the logbook (Fig. 5.9).

5. Diagnostic Yield

Fig. 5.6 (**a**) Tracheal stenosis protocol (**b**) Tracheal stenosis protocol

MANAGEMENT OF TRACHAEL STENOSIS

All patients who come in for evaluation of Tracheal Stenosis will have the following management program:

A. Time of consultation:

1. A formal consultation
2. Spirometry with flow volume loops will be preformed at the time of the initial consultation.
3. An NSF-36 questionnaire will be given to all patients to be filled out prior to any interventional procedures as a dyspnea index.
4. Nasal Swab for culture
5. A bronchoscopy with airway examination will be preformed.
   a. Airway cultures to be performed
6. Consideration of CT with 3D reconstruction for advanced imaging.

B. If the patient is required to go to the operating room the planned program will be:

1. Pseudoglottic Stenosis:
   a. Balloon dilation (2 minutes)
   b. Dumon stent placement
2. Cicatrical Stenosis:
   a. Laser radial incisions (KTP, 10W, 0.2 sec. duration, 0.5 sec. repeat
   b. Balloon dilation (2 minutes)
   c. Mitomycin-C application at interventionist's discretion, (60 sec. application).
   d. Dumon stent placement
3. Upon discharge:
   a. Patient will be placed on a nebulized Albuterol twice daily
   b. Patient will be placed on nebulized Mucomyst, 10%, 5cc once daily
4. Follow-up bronchoscopies will be preformed:
   a. One month post-stent insertion
   b. Three months post-stent insertion.
5. At the time of the surveillance bronchoscopy, all airway washings will be sent for bacterial cultures.
6. At the time of the surveillance bronchoscopies spirometry with flow loops volumes will be preformed.
7. NSF-36 questionnaire will be given post-stent removal to the patient at their one month follow-up bronchoscopy and spirometry.
8. All patients will be evaluated for stent removal at six months post initial stent placement. To include patient evaluation and spirometry, bronchoscopy at the interventionalists discretion.
9. If it is determined that the stent cannot be removed, surveillance bronchoscopy will continue every six months for one year and if there are no issues identified yearly after that.

Fig. 5.6 (continued)

MANAGEMENT OF TRACHAEL STENOSIS

10. If stent is removed:
    a. Bronchoscopy with flow loop volumes at week one post stent removal.
    b. Bronchoscopy will be preformed one month post-stent removal.
    c. Spirometry will be preformed:
        1. Pre-stent removal
        2. 1 week post stent removal
        3. 1 month post stent removal
        4. 2 months post stent removal
        5. 3 months post stent removal
        6. 6 months post stent removal
    d. Spirometry will be preformed at six months post-stent removal
    e. Follow-up bronchoscopy and Spirometry with flow loop volumes will be preformed one year after stent removal.
    f. No further scheduled evaluations.

In the past, most physicians were not held accountable to their diagnostic yield. In all reality, most pulmonologists who perform procedures do not keep personal databases and do the necessary statistics to assess their yields. The evaluation of diagnostic yield requires many parameters including on the agreement of terminology. "No cancer on this specimen" cannot be interpreted as "normal" or more correctly a true negative. Agreement between bronchoscopists, pathologists, thoracic surgeons, and any other member of the team assessing the patient must agree on acceptable terminology to distinguish between false negatives and true negatives. True positives and false positives can be more difficult as cryptogenic organizing pattern on pathology is a true diagnostic entity, but when found pathologically, when performing a transbronchial biopsies are acquired for a solitary pulmonary nodule, it could be the correct diagnosis (true positive) or be the tissue surrounding the mass and not the mass itself (false positive).

Agreement on terms for tissue processing is very important. If a lymph node is being sampled, it is unquestionably important for the pathologist to indicate if there are indeed cancer cells or not. But nearly as important is on the occasion that no cancer cells are identified, that it is communicated by the pathologist whether or not lymphatic tissue had been acquired, for example, normal lymphatic tissue present or target organ sampled. Appropriate reporting of this and reviewing these results then become paramount.

Without a comparison value, an individual yield though is of little value. Historical values from the literature can be found regarding the diagnostic yields of those who published them. The difficulty with this is that no regional, national, or international standards exist. Due to this, a small group of investigators formed the Interventional Pulmonology Outcomes Research Group (IPOR). The four investigators developed a database for the reporting of therapeutic procedures, looking at immediate and 30-day outcomes and complications. Agreements on terminology and further defining entities were accomplished, and keys were created; these terms was created and used for reporting (i.e., specific descritpoins of tracheal stenosis).

After the success of this project, after significant work with the American College of Physicians (ACCP), a new quality initiative was created, which after several years of work, became the ACCP Quality Improvement Registry, Evaluation, and Education (*AQuIRE)*. This international registry currently has modules for both diagnostic and therapeutic procedures. The AQuIRE databases main goal is "…to collect standardized multicenter data on various bronchoscopic interventional and diagnostic procedures." Data collected evaluates immediate and 30-day outcomes, diagnostic yields of all diagnostic bronchoscopic procedures, as well as outcomes of therapeutic procedures. As of this writing, the beta testing has been completed; the initial data was presented at the American College of Chest Physicians meeting, Chest, in Vancouver, British Columbia, in the fall of 2010. Manuscripts are now being prepared regarding the results:

(a) *System yields vs. individual physicians*: Programs need to be developed for individual hospitals, programs, or private practice groups to monitor the yields for procedures in their bronchoscopy suites as well as the individual physicians performing procedures. Programs such as pay-for-performance, reimbursement schemes are beginning to emerge and

Fig. 5.7 Labels at tissue preparation station in bronchoscopy suite

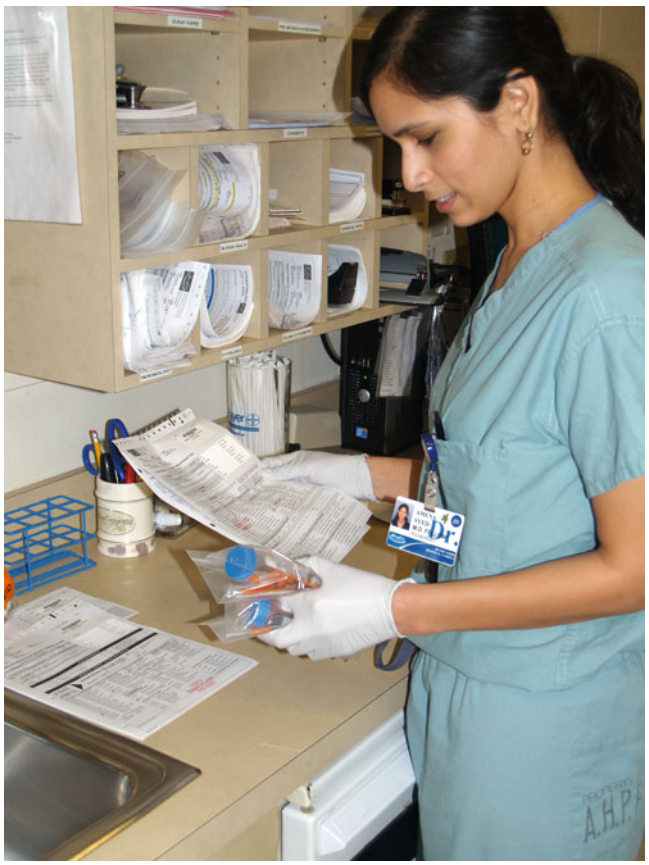


Fig. 5.8 Physician reviewing processed specimens

could have significant financial benefits or detriments to programs with this information (Focus).

(b) *Privileges*: Privileges are written by individual hospital systems. No local, regional, or national standards exist. With closer scrutiny, regulating bodies are also evaluating these practices. As with accreditation, privileges are often number based. Unfortunately, this practice does not identify potential limits in physicians' skill sets. Diagnostic yield evaluation with detailed M&M can serve as excellent quality control systems. An individual needs to be given the necessary time and training and have the commitment to accomplish this (Analyzed).

(c) *Retraining*: It is only through the above that individual skill sets that require additional or retraining will be identified and can be instituted (Developed and Executed).

6. Complication Rates

Complication rates in a bronchoscopy suite are most typically referred to as pneumothorax rates, rates of bleeding, etc. As quality control systems are developed, a variety of new issues will be identified and can be corrected. It is through registries and tools such as the AQuIRE database that these problems will be identified; standards for "acceptable" complication rates can be established as norms to be compared and contrasted to:

(a) *Thirty-day morbidity and mortality*: In most operating room or endoscopy centers, patients are frequently contacted the day after a procedure. Experience gained from the IPOR database and AQuIRE have demonstrated the importance of 30-day morbidity and mortality data to overall programmatic quality control.

(b) *Stents*: As an example of this, in some very active interventional pulmonology programs, a significant number of stents can are placed. It is only through close monitoring of immediate and 30-day morbidity that problems can sometimes be identified:

i. *Problem*: During weekly reviews of patient activity and 30-day results, it was identified that an increased number of patients had been returning for problems with recently placed stents.

ii. *Focus*: All patients with stents placed in last one year were reviewed with prospectively collected data.

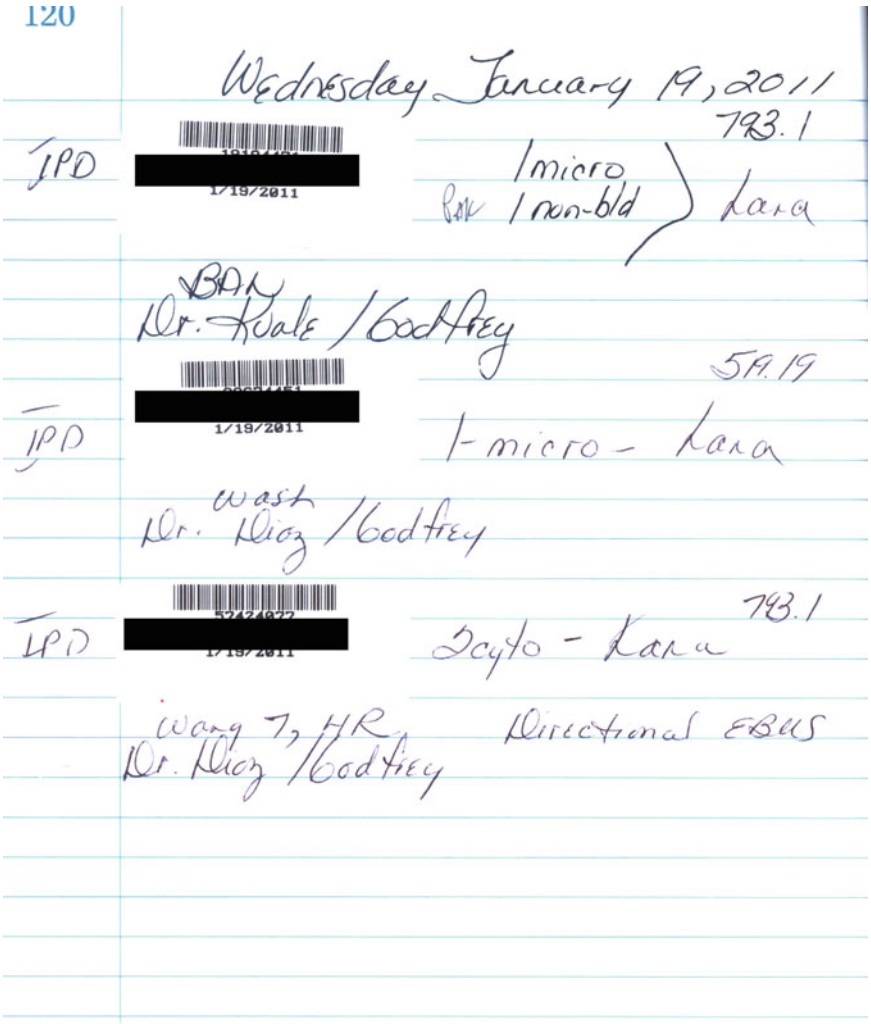


Fig. 5.9 Sample page from logbook

iii. *Analyze*: It was identified that patients with a new type of Y stent placed were returning with post-placement complication rates increased from 6 % (standard) to 72 % in this population.
iv. *Develop*: All patients were contacted and offered to have the stent removed and replaced.
v. *Execute*: 89 % of patients agreed to allow replacement of their stents, patients that had not manifested increased problems were also included.
vi. *Evaluate*: Poststent placement complications returned to less than 6 %; it was suspected that the new stents (new material) had been the primary causative factor. The stent use was discontinued; the company representatives were contacted and met with, presenting all data. A letter was sent to the Federal Drug Administration regarding concern for the stent use.

This example illustrates the use of systematic quality control issues demonstrating that incorporation of 30-day outcome data can significantly improve programmatic outcomes and patient safety.

B. Equipment Use in Procedures

Quality control must include the equipment involved in endoscopic procedures. The operational standards that are set for the use of equipment and the monitoring of this equipment are paramount to appropriate quality control for a bronchoscopy service. The following are some areas that can be addressed in a general bronchoscopy unit:

1. *Equipment quality control (function and calibration)*: An active system of reporting problems with equipment needs to exist to have a well-operating bronchoscopy service. If a bronchoscope is broken, it cannot be used and most likely will be taken out of service for repairs, but when a monitor malfunctions, or image distortion is identified on an ultrasound image, a formal system for reporting these problems with a program for reviewing these issues and insuring that they are corrected is necessary for a successful operation.
2. *Monitoring damage*: When directing a bronchoscopy unit, it is vital that all bronchoscopy damage reports and repairs are collected and reviewed. Patterns of damage can be ascertained if this is done routinely, identifying

physicians, nurses, or trainees as potential individuals leading to problems. An example of this would be the use of the endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) bronchoscope. One of the times that the bronchoscope is most prone to damage is when the tip of the bronchoscope is being flexed while the needle is being pushed through the working channel. When repeated damage has occurred, identifying the individuals involved, whether it is proceduralists, assistants, or processors, a pattern is usually evident. By observing the individual(s), a correctable problem can often be identified. In the above example, a physician did not want to lose contact with the wall of the airway and thereby lose their ultrasound image. They were therefore maintaining hard flexion while pushing the needle through the working channel of the bronchoscope, resulting in an unacceptably high number of damaged bronchoscopes. With identification of the problem and reeducation of the individual, the pattern was corrected.

Damage report monitoring can also be helpful to a bronchoscopy director for the replacement of older equipment. There is no recommended number of uses for a bronchoscope before it needs to be retired. By monitoring the damage reports, it will be evident when an increasing number of repairs will begin to occur. The bronchoscope can soon become more expensive than its actual value. If these damage reports are monitored closely, this information with the number of cases that the bronchoscope had been used can give the bronchoscopy director significant data to meet with administrators for capital investment of new equipment.

C. Other

1. Quality Control of Peripherals: There are a significant number of different brushes, forceps, needles, and other peripherals that are used in the bronchoscopy suite. Different practitioners often have individual preferences for these tools. Quality control programs to determine an effective selection of these devices will streamline operations by minimizing variances in purchasing, storage, and maintaining stock.
2. Data Storage: Endobronchial ultrasound, autofluorescence images, fluoroscopic images, pictures, or video taken during bronchoscopic procedure are all currently available. The appropriate use and storage of this data will become paramount to bronchoscopy suite operations. Currently, storage of such images is necessary for radiologists to bill for these procedures. With continued monitoring, it is more when not if that bronchoscopists will be asked to do the same thing.
3. Reprocessing and Equipment Storage: As was given in the example above dealing with the Johns Hopkins University, monitoring of the reprocessing of all bronchoscopes is immensely important. It is only through this monitoring that quality issues can be ascertained and quality control projects developed to deal with them.
4. Patient/Employee Safety: The science of human performance engineering evaluates workplaces to identify areas of concern for both patients and employees. Through close assessment, all workplaces have areas that can be improved upon. This can include the height of work spaces, the safety of the floor from cords, etc., or patient evacuation plans. Many of these areas are excellent for quality control projects.
5. Financial: The financial stability of any operation is important for its success. Leaders of bronchoscopy units must ensure that all operations are managed in the most efficient patterns possible. This can be accomplished by regular review of billing practices, both internal to the bronchoscopy unit itself as well as external billing personnel who work for hospitals or other systems that the bronchoscopy unit is affiliated with. An example of this was during one such review, it was identified that the hospital billers were billing only single station coding for transbronchial needle aspirations (TBNA) even when multiple stations were being sampled. The rationale was that the bronchoscopy note indicated which stations were being sampled. The billing codes 31629 and 31633 were associated with lobes of the lung, not lymph node stations. This led to the development of a system of associating lymph nodes with anatomically correct lobes. This has significantly improved upon bronchoscopy billing and reimbursement. Improving billing creates a financially sound unit, with more ability to access equipment capital or support for personnel for long-term improvements to the program.

Implementation

Creating quality control programs is a time-consuming and difficult process. It requires the initial consideration, project design, and resources for its development. Even with all of the correct tools being incorporated into the establishment of a quality program, implementation is and will always be the most difficult aspect of the project. Quality monitoring will require an increased amount of time and work from all employees involved. This will include physicians, nurses, respiratory therapists, and any other personnel. Before implementation can occur, all personnel must "buy into" the necessity of this type of program.

Implementation requires several steps. First, choose a project that can be accomplished in a short time frame. If the initial project will get results in several years of data collection, the likelihood of overall success is very low. Next, involve all staff when determining the scope of the project being created ensuring that the outcome will eventually affect all personnel involved. When completing a project,

whether it be work environment, funding, or patient and employee safety and satisfaction scores, immediate feedback to employees will create a culture in the endoscopy suite that identifies the importance of quality control projects.

The tools for data collection need to also be created prior to full implementation of the project. The project leader must ensure that each individual that will be imputing data has had the opportunity not only to use the tool but also to edit the format or the data points to make their job easier, yet still accomplish the goals set forth. By allowing this cooperative creation of tools, there is with higher likelihood that personnel will use the devices that they helped create.

Identify those individuals that may have a passion for the topic that is being evaluated. Recruit these individuals into a quality control team. Having personnel throughout all levels of an endoscopy suite (physicians, nurses, technicians, etc.) will allow greater visibility and more use from the team in general. Remember diligence in the implementation process. The director must always follow up on all aspects of the project. If the director allows the project to go fallow, so will the entire program.

Conclusion

This chapter highlights areas that quality control can be effectively used. Examples were given to illustrate practical application of theoretical ideas. Several tools are explained in this chapter that the leadership of a bronchoscopy suite can consider for application to their quality control programs. Quality control in a bronchoscopy suite is a very complex process. The most important step is that the leadership of the unit realizes the necessity of such a program. Initially, it requires champions of quality that can identify areas of concern and foster the support to collect the appropriate data to be analyzed. Quality control programs require strategies of approach to problems, which must be standardized to allow for a long-term program that will successfully guide the bronchoscopy suite to an effective, efficient, safe, and financially strong unit.

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Moderate and Deep Sedation Techniques

6

John Pawlowski

Introduction

The perfect anesthetic provides patient comfort and patient safety, while allowing the interventional pulmonologist complete access to the airways. Patient comfort, however, requires the inactivation of pain filters and airway reflexes from the oropharynx to the distal bronchi. Discomfort during airway manipulation is associated with coughing, vomiting, bronchospasm, and laryngospasm as well as hypertension and tachycardia. All of these responses can put the patient at risk and jeopardize the planned procedure. This chapter will focus on the techniques used to anesthetize the airway and the sedative, analgesic, and anxiolytic medications that can be used to facilitate patient comfort and cooperation. Specifically, this chapter will address techniques of moderate sedation and deep sedation. Awake (topical) methods and general anesthesia will not be discussed.

The techniques of moderate sedation and deep sedation both represent a balance between the judicious use of local anesthetics and adjuvant sedatives. Local anesthetics can either be applied topically or can be injected near nerves which innervate the upper airway. The nerve blocks can include the sphenopalatine, the glossopharyngeus, and the superior laryngeal nerves. These blocks are beyond the scope of this chapter. The nerve blocks and injection techniques are often uncomfortable to the patient, require multiple steps, and have been associated with risks of bleeding, airway closure, and even death. Instead, most of the airway to be visualized can be anesthetized using topical anesthesia.

Several techniques exist to apply local anesthetic directly to the airway mucosa. The most simple is to ask the patient to "swish and swallow" several milliliters of 2% viscous lidocaine solution. This technique can be used to numb the mouth, tongue, and oropharynx. Another method involves a nebulizer and allows the patient to breathe nebulized 4% lidocaine in 10 ml increments. Various atomizers and sprays are available as well to anesthetize the posterior pharynx. One of these sprays contains benzocaine, and, while it can be an effective anesthetic agent, it does have potential toxic side effects.

The most popular method to provide topical anesthesia during bronchoscopy is the "spray as you go" method. In this method, lidocaine is directly sprayed through the working channel of the bronchoscopy. Usually, 1–2% lidocaine is used above and on the vocal cords, and 2% lidocaine is employed to anesthetize the trachea and bronchi. For the nasal approach to bronchoscopy, pulmonologists often use 4% cocaine solution. Therefore, several types of local anesthetics can be used to successfully anesthetize the airway.

Toxic effects from local anesthetics can occur both due to cumulative systemic levels and also due to drug-specific effects. The symptoms and signs of local anesthesia toxicity are listed in Table 6.1. All of the local anesthetic agents have published maximal doses and the commonly used ones are listed in Table 6.2. Note that the route of administration can lead to an apparent relative margin of safety. For example, as much as 90% of the local anesthetic in a nebulizer never comes in contact with the airway mucosa, as it remains in the oropharynx or is exhaled into the atmosphere.

Several local anesthetics have specific side effects. Cocaine, for example, acts as a sympathomimetic and can lead to hypertension, tachycardia, coronary vasospasm, and myocardial infarction. Benzocaine, which is metabolized in the blood, can lead to the formation of methemoglobin, which is toxic at levels above 70%. Methemoglobinemia can result in cyanosis, arterial desaturation, and death. As little as a single spray of benzocaine has resulted in toxic levels of methemoglobin. The treatment for methemoglobinemia involves supplemental oxygenation and the use of intravenous methylene blue. Thus, cocaine and benzocaine are associated with serious side effects – side effects that require judicious use and deserve cautious practice. In our department,

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Table 6.1 Symptoms and signs of local anesthesia toxicity

Metallic taste
Tinnitus
Light-headedness
Anxiety
Somnolence
Seizure
Coma
Cardiovascular collapse
Death

Table 6.2 Maximum allowable doses of local anesthetics

LA		Effects
Cocaine	1.0 mg/kg	Hypertension, tachycardia, MI
Lidocaine	5.0–7.0 mg/kg	Seizure, ventricular arrythmia, coma
Benzocaine	1–2 sprays	Methemoglobinemia

we almost never find cocaine necessary and infrequently rely on benzocaine.

While the side effect profile as well as the substance abuse potential for cocaine may preclude its regular use as a local anesthetic, benzocaine remains valuable in every day bronchoscopic practice, due to its rapidity of action. The vasoconstrictive advantages of cocaine can be achieved with such agents as phenylephrine nasal spray, making cocaine less essential. Therefore, the therapeutic use of cocaine in interventional pulmonary procedures may have days that are numbered.

Overview of the Range of Sedation

Moderate and deep sedation represent the middle range of a spectrum of anesthetic depths that include light sedation (or anxiolysis), moderate sedation (or conscious sedation), deep sedation and general anesthesia (see Table 6.3). The differences in the sedation depth are evident by the difference in the way that patients respond to stimuli. Under moderate sedation, for example, patients demonstrate preserved protective airway reflexes. Also under moderate sedation, patients show appropriate responses to verbal or light tactile stimulation. Under deep sedation on the other hand, the patient may lose the protective airway reflexes and may not respond to verbal or light tactile stimuli. Patients under deep sedation may respond to repeated or painful stimuli. The choice to use either moderate or deep sedation techniques depends on the procedure planned, the experience of the pulmonologist, the experience of the sedation nurse or anesthetist, and the patient's comorbidities and concerns.

Studies that look at whether sedation techniques can improve bronchoscopic procedures are conflicting. Some studies show that moderate sedation can improve the patient outcomes for bronchoscopic procedures. Other studies show no improvement. One study by Putinati et al. identified as much as half the serious complications as coming from unwanted effects of the sedation. From a review of the literature, one can conclude that there is no conclusive evidence to argue for the administration of one sedation technique over another. The final decision must include the consideration of the safety and comfort of the patient, the experience of the pulmonologist and the anesthetist, and the anatomic requirements of the procedure.

Requirements to Provide Sedation

In the United States, the Joint Commission requires that all clinicians who administer sedation for interventional pulmonary procedures adhere to nine standards:

1. A presedation patient assessment is performed.
2. The sedation risks and options are discussed.
3. Moderate or deep sedation is provided by qualified personnel.
4. Moderate or deep sedation planes are written as a set of sedation orders.
5. Each patient's physiologic status is monitored during the sedation.
6. Each patient's physiologic status is collected and analyzed.
7. Qualified personnel are used to provide moderate or deep sedation.
8. Each patient's postprocedure status is assessed on admission to and before discharge from the postsedation recovery area.
9. Qualified personnel are used to discharge patients from the postsedation recovery area, and this should be according to criteria approved by the medical staff.

The presedation assessment requires a standard history and physical exam with certain information that directly relates to the safe conduct of moderate or deep sedation. This information includes:

1. Assessment of the airway.
2. Evaluation of comorbidities that could negatively affect the safety of the sedation plan. Any prior reaction to sedation will be noted.
3. Determination of the ASA physical status score.
4. Determination that the patient has complied with NPO guidelines. These guidelines are often institution-specific. We use NPO from solids for 6 h and NPO from clear liquids for 2 h prior to the procedure, unless the patient has a reason to have a full stomach (trauma, reflux, hiatal hernia).
5. Determination that the patient has a reliable escort home (if outpatient).
6. Consent for sedation.

Table 6.3 The range of depths of anesthesia

Analgesia	Minimal	Moderate	Deep	GA
Minimal sedation	Moderate sedation	Deep sedation	General anesthesia	
Preserved airway reflexes	Preserved airway reflexes	Protective reflexes may *not* be preserved	Reflexes *not* preserved	
Appropriate response to verbal stimulus	Appropriate response to verbal or tactile stimulus	Unable to respond to verbal or light tactile stimulus		
		May respond to repeated or painful stimulus	No purposeful responses to painful stimulus	
Spontaneous ventilation	Spontaneous ventilation	Ventilation may be inadequate	Ventilation may be inadequate	
MAC			*GA*	

The assessment of the airway is crucial because it helps to identify those patients in whom maneuvers to establish airway patency and to perform intubation may be difficult. These maneuvers can become necessary if the patient becomes oversedated. The Mallampati classification is one method to categorize patients who may prove difficult to intubate. To perform this examination, have the patient open his or her mouth fully and extend the tongue without phonating. The extent to which the palate and tonsils are visible determines the Mallampati classification (Fig. 6.1):

- Class I: The entire tonsillar pillars are visible.
- Class II: The top half of the tonsillar pillars is seen.
- Class III: The base of the uvula is seen.
- Class IV: The hard palate is seen.

In addition to the Mallampati classification, there are several other anatomic predictors of difficult intubation and by inference, difficulty in rescue from oversedation. A receding mandible, limited mouth opening of less than 3.5 cm between the upper and lower incisors, pronounced overbite and/or an inability to prognath the jaw, a decreased thyromental or hyomental distance, a history of obstructive sleep apnea, and a history of a difficult or failed intubation. Patients who possess one or more of these anatomic predictors of a difficult intubation may benefit by having their sedation provided by an anesthesiologist.

Comorbid conditions can also influence the safety and conduct of moderate or deep sedation. A general assessment of the impact of comorbidities on operative mortality is the ASA physical status. Based on the patient's comorbid conditions and their impact on the patient's daily living, the ASA physical status consists of the following categories:

- Class I: No disturbances
- Class II: Mild to moderate systemic disturbances
- Class III: Severe systemic disturbance that impacts daily function
- Class IV: Life-threatening systemic disturbance
- Class V: Moribund, not expected to survive

While a general assessment is important, consideration of the risks and potential complications resulting from specific comorbidities must also be considered. Conditions that limit the patient's cognitive function such as stroke and dementia can make the patient more sensitive to sedative medications. Patients with severe COPD more often experience the side

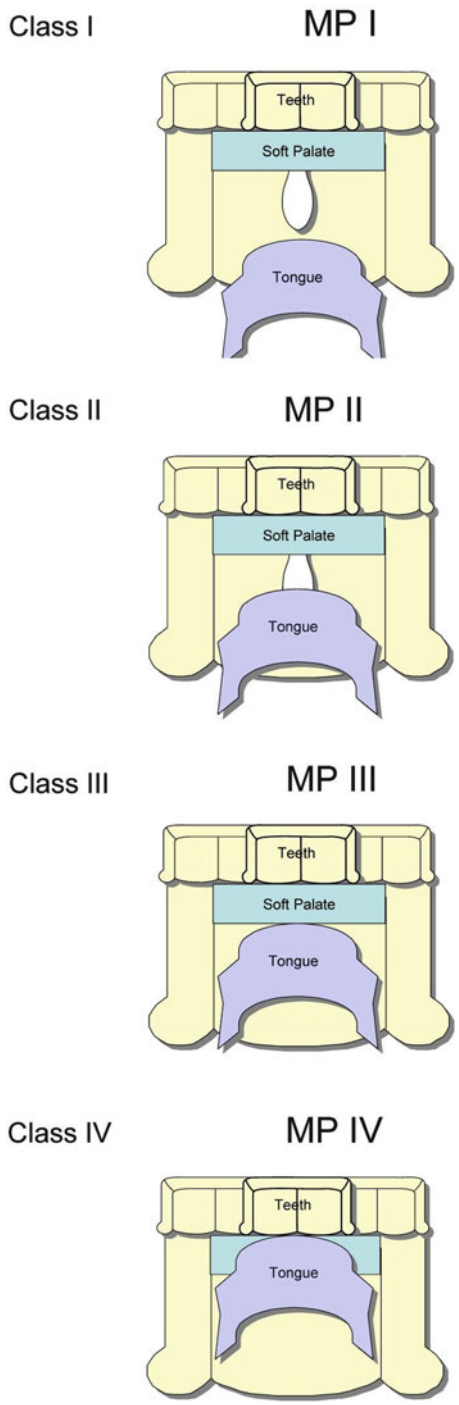

Fig. 6.1 Mallampati classification

effects of respiratory depression and respiratory failure due to opioids and benzodiazepines, for example. Cardiac problems such as uncompensated congestive heart failure and aortic stenosis can result in hemodynamic instability following modest doses of sedative/hypnotics. Liver and kidney disease can affect the metabolism and excretion of many drugs and can result in exaggerated and prolonged effects. While a detailed discussion of the specific effects of comorbidities is beyond the scope of this chapter, the pulmonologist should respect the potential problems that such comorbidities can present.

Equipment and Monitors

The safe provision of moderate or deep sedation requires the equipment necessary to provide the next deeper level of sedation, namely, general anesthesia. Such rescue equipment is listed in Table 6.4. The availability, functionality, and sterility (where applicable) of the equipment should be assessed regularly, and the providers of sedation should be familiar with the location of each item.

Although essential equipment is important, the most crucial element to providing safe sedation is a vigilant and trained sedation provider. This provider, if a nurse, should have no other significant clinical duties during the procedure and should have the same level of training and privileges in providing sedation as the physician performing the interventional pulmonology procedure. Inadequate monitoring of patients has been a frequent cause of adverse events during bronchoscopy. Vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation) should be recorded every 5 min along with level of consciousness and skin condition. Temperature should be documented at regular intervals. In addition, the timing and doses of individual drugs should be recorded along with the indications and effectiveness. The administration of intravenous fluids should be quantified. While the respiratory rate can be obtained through the measure of chest impedance using electrocardiogram electrodes, this author prefers the use of carbon dioxide monitors as a method to not only obtain respiratory rate but also to document the continuous production of CO_2 as well as the continuous patency of the airway (See Fig. 6.2).

Among the most difficult assessments for the provider of sedation are the adequacy of the airway and the depth of sedation. Chest movement may continue despite near total obstruction of the airway. The electrocardiogram may calculate normal respiratory rates despite absent alveolar ventilation. Observation of condensation on a face mask can occur from insufflation of the stomach. One solution to the problem of assessing the adequacy of ventilation is the use of end-tidal carbon dioxide monitors. This monitor has been shown to be nearly 100% sensitive in the detection of hypoventilation. Early detection of mild hypoventilation, on the other hand, can prevent subsequent hypoxemia. Thus, the use of carbon dioxide monitors can greatly increase the detection of hypoventilation and prevent the development of hypoxemia. In the patient undergoing moderate or deep sedation, the use of nasal cannula devices with side-port CO_2 detection can be employed with minimal discomfort to the patient and no disturbance to the proceduralist.

To monitor the level of sedation, the sedation provider must keep track of the patient's responses to verbal commands, sometimes in combination with light touch. Although the responsive patient would be expected to retain normal airway protective reflexes during moderate sedation, those reflexes can be obtunded by the use of topical anesthetic agents. Several semiobjective scoring systems exist to

Table 6.4 Equipment for moderate/deep sedation

Category	Specification
Intravenous access	IV fluids
	IV tubing, cannulae
	IV catheters
	Gloves
	Tourniquets
	Alcohol wipes
	Tape
Monitoring	Noninvasive blood pressure device
	Pulse oximeter
	Capnograph
	Electrocardiograph
Airway	Oxygen source, tubing, cannulae
	Bag/mask
	Suction
	Oral and nasal airways
	Laryngoscopes
	Endotracheal tubes
	Laryngeal mask airways
Emergency	Reversal agents (naloxone, flumazenil)
	ACLS medications
	Cardiac defibrillator

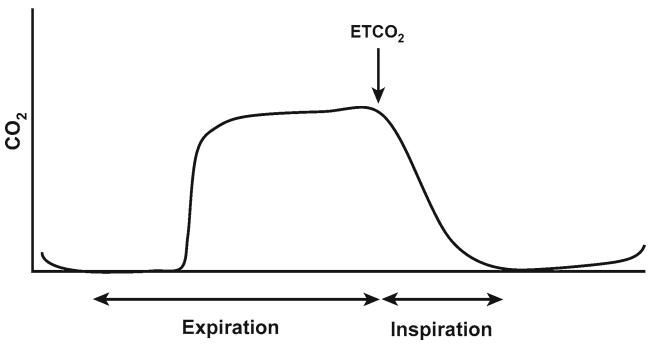

Fig. 6.2 Normal capnogram

document the patient's response to reproducible stimuli. The Continuum of Depth of Sedation Scale (CDSS), the Observer's Assessment of Alertness/Sedation Scale (OAAS), the University of Michigan Sedation Score (UMSS), and the Ramsay Score all provide a numerical scale of the level of sedation from alert to obtunded. All of these scores are subjective in their application but can be used to follow sedation trends.

More recently, a number of devices have been developed that attempt to quantify the level of sedation based on an analysis of the electroencephalogram (EEG). One of the most popularly used is the bispectral index. According to Rampil et al., the bispectral index is "a complex parameter composed of a combination of time domain, frequency domain, and higher-order spectral components derived from clinical data that measure the hypnotic component of an anesthetic." The bispectral index has been found to correlate fairly well with the level of sedation, to change appropriately in response to a change in the level of sedation, and to indicate inappropriately deep levels of unconsciousness. The bispectral index can be useful in maintaining moderate or deep sedation but is unable, at present, to help guide conscious sedation practices. Several reports have documented lower total sedation medication costs when a target bispectral index marker is used in the administration of both moderate and deep sedation techniques. Although touted as a monitor useful for the prevention of procedural awareness, the administration of both moderate or deep sedation should come with no guarantees of lack of awareness.

Postprocedure Recovery

All patients who receive either moderate or deep sedation should continue to be monitored in a postprocedure recovery area. Vital signs, including sedation levels, should be ascertained and recorded every 1–30 min at regular intervals. Although no specified total time for recovery exists, patients should remain in the recovery area until specific recovery benchmarks are met. Those patients who have received sedative reversal agents such as naloxone and flumazenil should remain an extra 2 h to avoid resedation after the reversal agent has been metabolized. Objective evidence of recovery can be quantified by scoring systems such as the postanesthesia recovery (PAR) test developed by Aldrete. The Aldrete score assigns points to the activity level, consciousness, circulation, respiration, and oxygen saturation. Given 0–2 points in each category, a patient must receive 9 or 10 points to be sent to an inpatient unit. A second Aldrete score is used to determine the patient's ability to be discharged to home. This postanesthesia discharge (PAD) test assigns 0–2 points for the dressing, pain, ability to drink, ability to walk, and ability to urinate. Patients must receive a total of 18 points or more from the PAR plus PAD to be discharged to home. Currently in use in dozens of countries, these Aldrete scoring systems are accepted by the Joint Commission in the United States. Prior to discharge, patients should receive both verbal and written instruction as well as a 24–hour contact number. The instructions should address diet, level of activity, and medications.

Medications

Introduction

During optimal moderate sedation, the patient is comfortable, sleepy, amnestic, and stable hemodynamically with modest doses of medications. During difficult sedations, the patient is agitated, semiconscious, uncooperative, tachycardic, and partially obstructed. Choosing the sedative medications to achieve optimal results requires an understanding of the kinetics and the effects of each agent along with its potential side effects. Often, patience is needed to deliver divided doses and to titrate to effect. This section will outline the commonly used medications (refer to Table 6.5) in the delivery of moderate and deep sedation to patients who are undergoing airway procedures.

Benzodiazepines

Midazolam is the most appropriate and commonly employed benzodiazepine for moderate sedation. The effects of anxiolysis, amnesia, and sedation make midazolam an ideal drug for moderate sedation during short procedures that have minimal painful stimulation. Usually given intravenously, midazolam can also be given orally, intramuscularly, or rectally. Midazolam is not diluted in propylene glycol, as with other benzodiazepines, and thus, does not have as much pain on injection and has a lower incidence of thrombophlebitis. In sedative doses, midazolam produces drowsiness in 2 min and has a therapeutic half-life of 30 min. Usual intravenous doses are 1–2 mg iv q5 min until desired sedation is achieved.

Table 6.5 Medications used in moderate and deep sedation and ongoing adult dosing schedules

Drug	Dose	Onset	Duration
Bolus type			
Midazolam	5–2 mg	2 min	30 min
Fentanyl	25–100mcg	5 min	30 min
Ketorolac	15–30 mg	30 min	4–6 h
Infusion type			
Propofol	25–100 mcg	1–2 min	–
Remifentanil	0.1–0.3 mcg/kg/min	1–2 min	–

As with all benzodiazepines, midazolam produces its effect by acting on the gamma-aminobutyric acid (GABA) receptors by enhancing the receptor affinity for GABA. The action of GABA is to produce anxiolysis and sedation. Other drugs that also act on GABA, such as barbituates, etomidate, and propofol, can act synergistically to enhance the effect of midazolam.

Anterograde (not retrograde) amnesia is an important effect of all benzodiazepines, and the amnestic effects can be out of proportion to the sedative effects. For example, a patient may appear alert and conversant but may forget all postoperative conversations and instructions. Since the storage of the events in the patient's memory occurs after the administration of midazolam, it is correctly termed anterograde amnesia.

Midazolam should be used with caution in elderly patients or in patients with known cognitive deficits. In addition, midazolam is highly protein bound and is metabolized by the liver, making patients with liver failure more susceptible to exaggerated effects and prolonged duration of sedation. Intravenous doses in the setting of advanced age or hepatic failure are .5–1 mg iv q5 min until desired sedation is achieved. Agents that alter the activity of cytochome P450 can also affect the action of midazolam. The effects of midazolam can be reversed by flumazenil, which will be discussed later.

Propofol

Propofol has emerged as a versatile and effective sedative in the practice of moderate and deep sedation. As the most commonly used parenteal anesthetic agent in the United States, propofol is a substituted isopropylphenol that is insoluble in water and is usually prepared in a lipid emulsion for intravenous administration. The emulsion includes soybean oil, egg lecithin, and glycerol, and allergic reactions to the emulsion have been reported. Either disodium ethylene diamine tetraacetic acid (EDTA) or sodium metabisulfite is added as a preservative to inhibit bacterial growth, but the propofol mixture does support bacterial proliferation, and serious infections have been reported. Currently, the practice in the United States is to discard any propofol drawn into a syringe within 6 h.

Propofol acts on the GABA receptors in a mechanism similar to the benzodiazepines and other sedative/hypnotics. In addition to metabolism by cytochome P450 in the liver, propofol also has extensive nonhepatic metabolism as well as tissue uptake. As a result, the context-sensitive half-time is not prolonged in infusions lasting longer than 8 h, in cirrhotic or alcoholic patients, nor in patients with renal failure. Propofol concentrations are elevated and prolonged in the elderly, however, and the elderly often demonstrate significant hypotension following bolus administration of propofol.

Propofol produces rapid sedation and rapid return of consciousness without associated nausea or vomiting. Usual doses of propofol in the healthy patient are 30–150 mcg/kg/min by intravenous infusion or 10–20 mg iv q 3 min prn desired level of sedation. Side effects of propofol include hypotension, apnea, and airway obstruction, so close hemodynamic monitoring and immediate access to airway interventions is needed. Especially useful in pulmonary patients, propofol does not provoke bronchospasm. Propofol does cause pain at the injection site, but this can be ameliorated by pretreatment with 1% lidocaine. The use of propofol by nonanesthesia providers is controversial, and many states require that the sedation provider be certified in sedation techniques and competent in emergency airway management.

Severe lactic acidosis resulting from prolonged propofol administration has been reported in both adults and children. This "propofol infusion syndrome" (PIS) has been recently described during shorter durations of propofol use. Any unexplained tachycardia while on a propofol infusion should be a suspected case of propofol infusion syndrome – an arterial blood gas and serum lactate should be drawn. Other causes of metabolic acidosis, such as DKA, sepsis, and hypochloremic metabolic acidosis from extensive infusions of normal saline, should be excluded. The mechanism of PIS appears to be the interruption of the electron transport chain and the impairment of long-chain fatty acid metabolism.

Dexmedetomidine

An adjunctive agent for moderate and deep sedation procedures is *dexmedetomidine*. Having sedative, hypnotic, and analgesic properties, dexmedetomidine is the d-enantiomer of medetomidine, an imidazole subclass alpha-2 agonists. Soluble in water, dexmedetomidine does not cause pain on injection and, after a single bolus, has a half-life of 2–3 h. There is a substantial context-sensitive half-time change, however. Following a 10-min infusion, there is a context-sensitive half-time of 4 min, but after an infusion of 8 h, that context-sensitive half-time extends to 250 min. There is little to no respiratory depression with dexmedetomidine, and there is no hyperalgesia or allodynia noted on withdrawal of this medication. An infusion of 0.7 mcg/kg/min will generally achieve a BIS number of 70–80 within 20 min. Thus, for longer pulmonary procedures, dexmedetomidine can be a useful intraoperative adjunct and can provide some postoperative analgesia.

Opioids

From both natural and synthetic sources, the opioids include dozens of medications whose utility in moderate and deep sedation is determined by its efficiency and duration of action. All opioids act on the mu receptors, and this agonist activity accounts for the properties of analgesia. While the analgesic and antitussive action of opioids are clinically

useful during interventional pulmonology procedures, the side effects of nausea, vomiting, itching, muscle rigidity, and respiratory depression are undesirable. Fentanyl, for example, exhibits chest wall muscular rigidity more often that the other synthetic opioids. In certain cases, chest wall rigidity can be so severe as to impair ventilation and require the use of neuromuscular blocking agents (paralytics) to overcome the restriction in thoracic excursion. To prevent the nausea and vomiting caused by opioids, on the other hand, the preemptive use of antiemetics has been shown to be effective.

To be effective in the practice of moderate or deep sedation, opioids should have a strong efficacy and rapidly reach equilibrium concentrations. Both fentanyl and remifentanil possess these properties. Fentanyl is lipid-soluble, highly protein-bound, and metabolized by the liver. Lipid solubility facilitates the movement of fentanyl across the blood–brain barrier, making the time to peak analgesic effect following a single iv bolus a short 5 min. A single bolus of fentanyl will last 30 min. Most of the initial bolus of fentanyl is bound to inactive tissue sites in lung, fat, and skeletal muscle. As tissue sites become saturated by either repeated boluses or by continuous infusion, however, the context-sensitive half-time becomes longer. Thus, with continued administration of fentanyl, the half-time approaches the elimination half-life of 3–4 h. As the duration of the procedure requires repeated boluses or continuous administration of fentanyl, therefore, fentanyl no longer behaves as a short-acting agent. To counteract the residual effects of opioids, certain narcotic antagonists do exist and will be discussed later.

An alternative opioid to fentanyl that can be used for both short and long duration procedures is remifentanil. Remifentanil is a synthetic opioid with equivalent potency to fentanyl: both are 100 times more potent than morphine. An intravenous bolus of remifentanil has a rapid onset of 1–1.5 min. Unlike the other synthetic opioids, remifentanil is metabolized by plasma esterases. The elimination half-life of remifentanil is about 9 min and is independent of liver or kidney function. Repeated doses or continuous infusions of remifentanil do not prolong the elimination half-life. A 5-h infusion of a high-dose remifentanil, for example, showed return of spontaneous ventilation within 3–5 min. Such rapid elimination means that remifentanil does not provide any residual analgesia in the postoperative period, requiring other analgesics in the recovery room.

It is important to remember that all opioids provide intense pain relief without loss of proprioception or consciousness. While this property of opioids brings comfort to millions of patients, it can also result in awareness. Intraoperative awareness is a recognized complication of general anesthesia, and one that is more common when opioids are used. Awareness during moderate or deep sedation, however, should be an expectation. It is essential that every proceduralist and sedation provider advise the patient that some degree of recall is possible and even likely. Monitors such as the bispectral index device can help assure a consistent level of sedation but cannot prevent awareness nor can it guarantee amnesia.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs share the three properties of analgesia, antipyrexia, and anti-inflammation. As a large and heterogeneous class of medications, the NSAIDs block both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The only NSAID with real application to moderate or deep sedation is ketorolac. Ketorolac can be administered intravenously and provides rapid pain relief. As a COX-1 antagonist, however, ketorolac can cause gastric irritation and ulcers and can inhibit platelet function. Ketorolac does not cause respiratory depression, however, nor does it produce tolerance. In patients with a history of aspirin allergy, nasal polyps, or asthma, ketorolac has triggered life-threatening bronchospasm. In addition, patients with a history of congestive heart failure, hepatorenal syndrome, or hypovolemia may be susceptible to ketorolac-induced renal failure due to their dependence on the local production of prostaglandin to maintain renal blood flow. A single bolus of ketorolac provides pain relief within 30 min, and the analgesic effect lasts 4–6 h.

Reversal Agents

Reversal agents, while intended to counteract the unwanted or prolonged effects of other agents, come with their own problems. An understanding of the chemical properties, kinetics, binding characteristics, and elimination pathways are essential to predicting clinical situations that occur during the use of reversal agents.

To reverse the unwanted effects from benzodiazepines, flumazenil can be used. Flumazenil, an imidazolebenzodiazepine, binds with high affinity to the GABA-A receptor, acting as a competitive inhibitor. Showing slight activity, flumazenil acts as a reverse agonist at low concentrations and an agonist at high concentrations. Despite the agonist activity of flumazenil, however, it does not prevent withdrawal symptoms. Dysphoria, irritability, dizziness, unpleasant dreams, anxiety, insomnia, anorexia, sweating, tremors, and frank seizures have been reported from flumazenil use. Flumazenil is not recommended in those patients who are taking antiseizure medication. Usually, 1–5 mg of flumazenil is given in divided doses every 1–10 min until a desire level of consciousness is achieved. The effects last 30–60 min, so the potential for resedation is possible. In practice, benzodiazepine overdose rarely causes respiratory depression, making the urgent need for flumazenil uncommon.

To reverse the effects of opioids, naloxone can be used. As a nonselective competitive antagonist, naloxone binds to mu, delta, and kappa opioid receptors. Used to treat narcotic-induced respiratory depression, naloxone can also reverse

opioid-induced analgesia as well. Postprocedure patients given naloxone can experience hyperacute, severe pain. In response to naloxone-induced pain, the sympathetic nervous system can become activated, and the patient can develop tachycardia, hypertension, pulmonary edema, and cardiac arrhythmias. Plasma cortisol and catecholamine levels rise following naloxone administration. Less explainable side effects from naloxone include dysphoria and decreased performance on memory tests. Given in divided doses of 1–4 mcg lkg, naloxone quickly reverses opioid-induced respiratory depression and has a duration of action of 30–45 min. The possibility of renarcotization exists, so continuous vital signs monitoring should be employed, while opioid reversal agents are being used. In summary, the use of naloxone should be as a rescue strategy to reverse respiratory or supplemental breathing measures are not practical or have not been beneficial in improving the clinical situation.

Antiemetics

In clinical practice, nausea and vomiting are an unpleasant and unintended consequence to anesthesia, inflammation, or motion that can add morbidity to the procedure and can complicate the recovery. The sensation of nausea and the act of vomiting are a coordinated set of autonomic, behavioral, muscular, and emotional responses. The coordination of the vomiting response occurs in the central emesis center in the lateral reticular formation of the mid brainstem in the area adjacent to both the chemoreceptor trigger zone (CTZ) and the nucleus solitarius of the vagal nerve. This complex neural connection requires a variety of neurotransmitter influences. Serotonin, histamine, acetylcholine, dopamine, and prostaglandins have key roles in neuromodulating this emesis center. Antiemetics, therefore, target one or more of these neurotransmitter systems. For example, ondansetron blocks serotonin, cyclizine blocks histamine, and scopolamine blocks acetylcholine. Cyclizine and scopolamine may be more useful when the vestibular system is the active trigger, such as in motion sickness. The steroid dexamethasone can reduce the influence of inflammation in inducing nausea. Benzodiazepines can suppress anticipatory nausea. Thus, the variety of antiemetics can be used alone or in combination to target specific components causing the nausea or to take advantage of synergistic effects from combination antiemetic strategies.

Complications from Moderate and Deep Sedation

Complications from moderate and deep sedation can occur during conditions of oversedation, undersedation, or idiosyncratic responses to "therapeutic levels" of sedation. Too much sedation can produce respiratory depression and hemodynamic collapse. Too little sedation can lead to excessive movement, delirium, and pain. Even patients receiving "optimal" levels of sedation can demonstrate allergic reactions or side effects such as chest wall rigidity, laryngospasm, and bronchospasm. "Optimal" levels of sedation can worsen underlying conditions such as acute intermittent porphyria, malignant hyperthermia, or carcinoid crisis. Specific complications can occur such as adrenal suppression from etomidate or rhabdomyolysis from propofol. This section will focus on the general problems that can result from moderate and deep sedation techniques.

Most sedatives have myocardial depressant effects and/or vasodilatory effects that can lower blood pressure. The degree of cardiovascular depression in response to sedation will depend on the patient's cardiovascular and volume status, the influence of residual blood pressure medications, and any surgical conditions that may affect the patient. For example, the reverse Trendelenburg position can drop preload and cause exaggerated hypotensive responses to sedative administration. As mentioned previously, comorbidities such as coronary artery disease, valvular heart disease, or cardiomyopathy not only increase the risks to the patient who is undergoing sedation but also can increase the degree to which the vital signs change in response to sedation.

Most sedatives blunt the ventilatory response to both high levels of carbon dioxide and low levels of oxygen. In large enough doses, most sedatives can cause apnea. For this reason, all patients who receive sedatives should be monitored for both ventilation and oxygenation. Ventilatory rates, however, can be misleading as they do not always correlate with minute ventilation. To better detect hypoventilation, either end-tidal CO_2 or minute ventilation should be measured for procedures that use moderate or deep sedation. To monitor oxygenation, the pulse oximeter provides a reliable measure of desaturation. Evidence of hypoxemia, however, does not usually occur in this setting until the patient has been hypoventilating for several minutes. To rescue patients from conditions of hypoventilation or hypoxemia, advanced airway equipment needs to be immediately available along with an enriched oxygen supply, continuous suction, and trained personnel.

The Future of Sedation: New Drugs and Strategies

A number of new drugs have been developed to reduce the side effect profiles and improve the safety margins in the administration of sedation. Several of these new drugs represent a new strategy, by which pharmacologic agents are designed to rapidly transform into inactive metabolites. This next section will introduce some of these new agents that may come into clinical use in the near future.

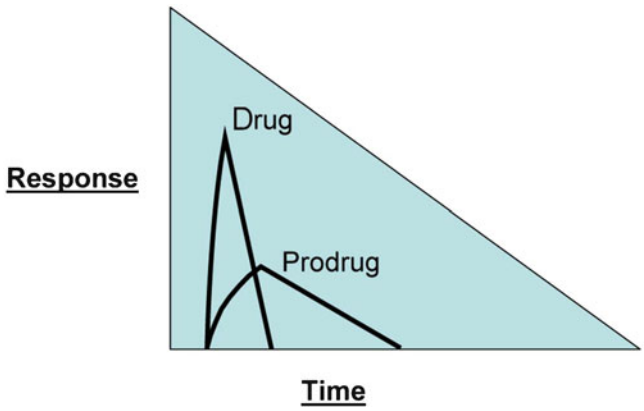

Fig. 6.3 Dose response of a drug versus a prodrug

In the earlier discussion of propofol, a number of disadvantages were enumerated; propofol causes a burning sensation when injected and produces dose-dependent cardiovascular and respiratory depression. In addition, the lipid emulsion can support bacterial growth and can result in high lipid levels during chronic administration. A potential alternative to propofol is the prodrug *fospropofol*. Fospropofol is a water-soluble prodrug that does not require a lipid emulsion and that does not result in pain on injection. As a phosphono-O-methyl prodrug of propofol, fospropofol must be metabolized by alkaline phosphatases to produce the action drug propofol. The requirement for metabolism makes the onset of activity of fospropofol delayed, when compared to propofol, and this results in lower peak concentrations (see Fig. 6.3). The lower peak concentrations of propofol mean that there is less cardiovascular and respiratory depression following a bolus of fospropofol than an equivalent bolus of propofol. Thus, for longer sedation cases, fospropofol may provide an alternative to propofol that has fewer side effects and a better margin of safety.

A modification of the sedative/hypnotic etomidate may present another opportunity to improve the side effect profile. *Methoxycarbonyl-etomidate (MOC-etomidate)* is an etomidate-like molecule that is vulnerable to nonspecific esterase degradation. Active at the GABA-A receptor, MOC-etomidate has a rapid onset of action and short duration. Unlike etomidate, MOC-etomidate does not show the side effects of adrenal suppression. Therefore, MOC-etomidate may be more suitable than etomidate in the chronically ill, adrenally suppressed patient, and this drug may be more appropriate for prolonged infusions, with less chance for accumulation of active moieties and adrenal suppression.

An ultrashort-acting benzodiazepine, CNS 7056, has been developed that also takes advantage of chemical modifications to make this compound susceptible to nonspecific esterases. When compared to midazolam, CNS 7056 demonstrates peak levels of sedation within 4 min versus 15 min for midazolam. Recovery from sedation by CNS 7056 occurs in 10 min versus 40 min for midazolam. The plasma clearance of CNS 7056 is threefold faster than midazolam. Aside from its faster rate of clearance, CNS 7056 is also metabolized in a method that is independent of liver cytochrome P450. The liver isozyme 3A4, which is needed for the degradation of midazolam, is affected by drug-drug interactions as well as by liver failure. The esterase mechanism of degradation of CNS 7056, by contrast, is independent of those drug interactions and not affected by liver failure. Currently demonstrated in nonhumans, CNS 7056 may represent a new benzodiazepine sedative with ultrafast kinetics and a robust system of metabolism and elimination.

The current trend for the development of sedative drugs is one of "soft drugs" – a term that refers to its rapid biotransformation into an inactive form or its intrinsic instability and fragility. Other soft drugs include remifentanil, with its degradation by esterases. Several nonsedative drugs also have "soft drug" characteristics such as succinylcholine with its vulnerability to butyrylcholinesterases (or pseudocholinesterases) and atracurium, a nondepolarizing muscle relaxant that spontaneously forms nonactive metabolites via the Hoffmann degradation. In all of these examples, "soft drugs" result in rapid and efficacious activity followed by almost immediate degradation and elimination. These types of medications may prove to be the backbone to future sedation techniques.

In conclusion, the use of moderate and deep sedation techniques can enhance the performance of interventional pulmonology procedures by improving the level of cooperation, reducing unwanted movement, improving relief from pain, and avoiding the complications of general anesthesia. To accomplish these sedation goals, the sedation provider needs to balance the desired effects of anxiolysis, analgesia, and sedation from the unwanted side effects. In preparation for sedation, all patients need a preoperative assessment, which includes a focused history and physical examination. The proper equipment, medications, and training can assure that the patient will enjoy a safe environment during the procedure and during the recovery. Advanced planning can make the challenges of patients with pulmonary problems, sharing airways with multiple specialties, and coping with sedation techniques when the patient is neither totally awake nor fully asleep predictable, pleasant, and safe for all involved.

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Physiology of Fixed Airway Obstruction

7

Ross K. Morgan

Introduction

This chapter will focus on fixed upper or central airway obstruction which may present to the interventional bronchoscopist for assessment and management. It is important to recognise this as it is commonly misdiagnosed and the physiological changes that occur can be detectable on pulmonary function testing. Fixed *airflow* obstruction is a term used to describe the consequence of airway remodelling in the face of unchecked inflammation in asthma or the irreversible small airway dysfunction seen in chronic obstructive pulmonary disease and will not be discussed here.

The causes of fixed upper airway obstruction are numerous and are listed in Fig. 7.1. In this chapter, I will describe the physiological changes that occur, demonstrating the effects on pulmonary function testing that may be useful in diagnosis and provide a number of illustrative cases. The normal airway anatomy and dynamics of airflow and airway resistance will first be described as a good working knowledge of these is required before considering the altered physiology of central airway obstruction.

Airway Anatomy

The upper airway is made up of three sections: the anatomic spaces of the nose, mouth and pharynx; the larynx; and the trachea. The larynx extends from the root of the tongue to the trachea and consists of three parts: the supraglottis, which includes the epiglottis and the false vocal cords; the glottis, which includes the vocal cords and surrounding structures; and lastly the subglottis, a 1.5–2-cm segment below the cords that is completely surrounded by the cricoid cartilage and below which the airway becomes the trachea.

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The trachea can be divided into two segments by the thoracic inlet; the shorter cervical trachea extends for the first 2–4 cm from just below the cricoid cartilage to the thoracic inlet. The intrathoracic trachea then continues for a further 7–9 cm until dividing into the right and left main stem bronchi at the main carina. The wall of the trachea contains up to 22 horseshoe-shaped cartilaginous rings that line the anterior and lateral walls and give the tracheal its shape. A membranous component which does not contain any cartilage completes the posterior wall.

The length and diameter of the trachea is roughly proportional to the height of the individual. In the adult male, the trachea is approximately 10–13 cm long with external diameters of 2.3 cm coronally and 1.8 cm sagittally. In women, corresponding tracheal dimensions are 2.0 and 1.4 cm. There are approximately 2 C-shaped rings per cm. The trachea has inherent flexibility and some elasticity; this significantly reduces with age as calcification of the rings occurs. In addition in the elderly as the vertebral height is reduced and kyphosis occurs, the trachea may take on a more horizontal course which can result in more likelihood of extrinsic compression. The cross-sectional horseshoe shape of the trachea can also be markedly altered in the elderly, in particular in those with COPD in whom the distal trachea becomes flattened from side to side, taking on a so-called sabre-sheath shape.

Trachea: Anatomic Relationships

When considering ways in which the trachea can get compressed or obstructed, it is worth reviewing the anatomic relationships of the trachea along its length. Throughout its course the trachea lies in close contact with the oesophagus which runs slightly to the left and behind the airway. Anteriorly, the thyroid isthmus crosses over the superior part of the trachea at the level of the second and third tracheal rings. At the tracheal midpoint, the brachiocephalic artery crosses over from the aortic arch to the right side. On the left lateral side, the aortic arch makes an impression on the left

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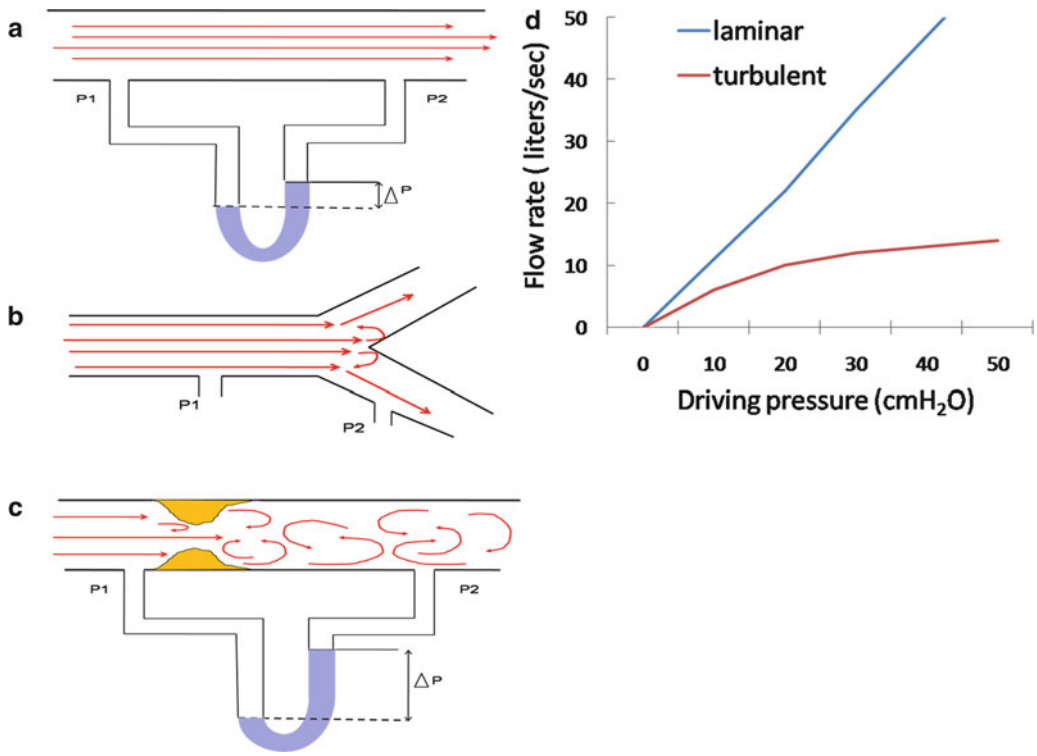

Fig. 7.1 Flow through tubes. (**a**), laminar flow. (**b**), transitional flow. (**c**), turbulent flow. (**d**), with turbulent flow, a higher pressure is required to maintain the flow rate, and the relationship between driving pressure and flow is non-linear

lower tracheal wall. The tracheal bifurcation is at the level of the fifth thoracic vertebra. Mediastinal lymph nodes lie adjacent to the airway wall in paratracheal, pre-tracheal and subcarinal locations.

Lower Airway Anatomy

Below the carina, the airways divide approximately 22–25 times before terminating in alveolar sacs, the functional unit of ventilation. The first 16–18 divisions make up the conducting airway passages of the human adult lung, and the remaining six or seven divisions are considered the respiratory zone composed of respiratory bronchioles from which alveoli bud from the walls. Finally, the airways terminate in the alveolar ducts which are lined with alveoli.

Physiology of Breathing

During inspiration, the thoracic cavity volume increases mainly due to diaphragmatic contraction and flattening and, to a lesser extent, through the action of the external intercostal muscles which raise the ribs, drawing air into the lung and down to the terminal bronchioles. This part of inspiration occurs with large velocity, and the pressure required to move gas along is very small as the airways are uniquely designed to conduct air to the terminal bronchioles. For instance, a flow rate of 1 l/s can be achieved with a pressure drop along the airway of less than 2 cm water. Thus, with the normal swings in intrathoracic pressure during resting ventilation of 3 or 4 cm water (change in intrapleural pressure from +2 cm to−2 cm water), air can move with considerable velocity down to the respiratory zones. Once air arrives there, the cross-sectional area of the acini, or functional respiratory units, is so large (50–100 m^2) and the distances so short that there is a rapid fall in velocity of inhaled air and rapid diffusion within the respiratory units occurs.

Accessory muscles of inspiration include the scalene muscles which elevate the first two ribs as well as the sternomastoids which can elevate the sternum to some extent. Associated small muscles that play a minor role include the alae nasi, which cause flaring of the nostrils, and some of the extensor neck muscles, all of which try to increase the diameter of the upper airway passages.

The compliance of the lung reflects the change in volume for unit pressure, and in health, the lungs are naturally very distensible with a compliance of about 200 l/cm water. Lung compliance increases in diseases such as COPD where there is reduction in lung elasticity due to tissue destruction

and emphysema. Reduced compliance is associated with conditions that make the lungs stiff, such as pulmonary oedema and pulmonary fibrosis.

Airway Resistance and Flow

Resistance can be defined by the mathematical formula:

$$R = \Delta P / V$$

in which R is resistance, ΔP is the pressure difference or driving pressure and V is the flow. It is expressed in cmH_2O/L/s. Resistance to airflow into the lungs as they expand is contributed to by intrinsic pulmonary resistance (e.g. elasticity) of the lungs and chest wall but mainly is accounted for by airway resistance, which makes up about 80% of the total resistance. As discussed above, the cross-sectional area of the lower airways is so great, and the branch points so numerous that resistance is almost negligible at the lower levels. Thus, most of the overall airway resistance comes from the upper airways from the level of the trachea to about the 7th generation bronchi. Within these larger airway tubes, resistance to flow is inversely related to the radius of the tube to the 4th power. Therefore, in the presence of fixed obstruction that narrows the airway radius by half, for example, a tracheal obstruction that reduces the lumen to 1 cm, a 16-fold increase in airway resistance results.

Air obeys the principles of fluid dynamics as it moves along the airways from higher- to lower-pressure areas. Flow can occur in three different patterns within the airways: laminar, turbulent and transitional with eddy formation at branch points or when encountering irregularities along the airway surface (Fig. 7.1). Laminar flow is streamlined with air in the centre of the tube moving fastest, and increasing driving pressures will increase flow proportionately. With turbulent flow, a higher pressure is required to maintain the flow rate, and the relationship between driving pressure and flow is non-linear (Fig. 7.1d). In normal conditions in most of the bronchial tree, the airflow is transitional.

Whether flow will be laminar or turbulent also depends to a large extent on the Reynolds number, Re:

$$Re = 2rvd / n$$

where d is density, r is radius, v is velocity and n is viscosity. Laminar flow occurs at low Reynolds numbers, while turbulent flow occurs at high Reynolds numbers. Low-density gases like helium tend to produce less turbulence. This underlines the utility of heliox, a mixture of 60–80% helium and 20–40% oxygen, in patients with central airway obstruction and respiratory distress. Helium has a density one-third that of nitrogen. By reducing the Reynolds number, heliox decreases the tendency for turbulent flow to develop and thereby results in an increase in flow for the same driving pressure, reducing dyspnoea and work of breathing. This may buy some time in initial management of central airway obstruction in the acute situation.

Measurement of Airway Obstruction: Pulmonary Function

Airflow is typically measured in the pulmonary function laboratory using the spirometer and through the generation of flow-volume loops. A flow-volume loop is created when the patient inhales deeply to a total lung capacity (TLC) and then forcefully exhales until the lungs have been emptied to the residual volume (RV) followed by rapidly inhalation again to reach the TLC. A typical normal loop is shown in Fig. 7.2a. The upper portion is the expiratory limb and has been well studied and found to contain a wealth of information on airflow obstruction, in particular for small airway disease in COPD. The inspiratory portion gets less attention but as discussed below can be particularly useful in observation of large airway obstruction. It should be noted however that forced inspiratory manoeuvres in particular are effort dependent and that reaching acceptability and repeatability criteria such as they exist for the inspiratory limb of the loop can be difficult. Additionally, most of the studies on the use of flow-volume loops in airway obstruction which are outlined below are observational and limited to small numbers of patients.

Flow-Volume Loops

The seminal work on the use of flow-volume loops in airway obstruction was published by Miller and Hyatt in the late 1960s. They proposed a classification based on pressure changes around the site of obstruction and identified three patterns from the contours of the flow-volume loop: (1) variable intrathoracic, (2) variable extrathoracic and (3) fixed obstruction. For these studies, they simulated airway obstruction by having normal subject's breath through tubes of increasing resistance (smaller diameter) and found that flow rates plateaued during inspiration and expiration and that plateaus were reached at lower flow rates as the resistances were increased Fig. 7.3.

During normal respiration, there are changes in transmural pressure along the tracheal length that impact on the calibre of the large airways. The extrathoracic airway is surrounded by positive atmospheric pressure, tending to collapse the airway during inspiration when tracheal pressure is negative. At the same time, the intrathoracic airway is surrounded by

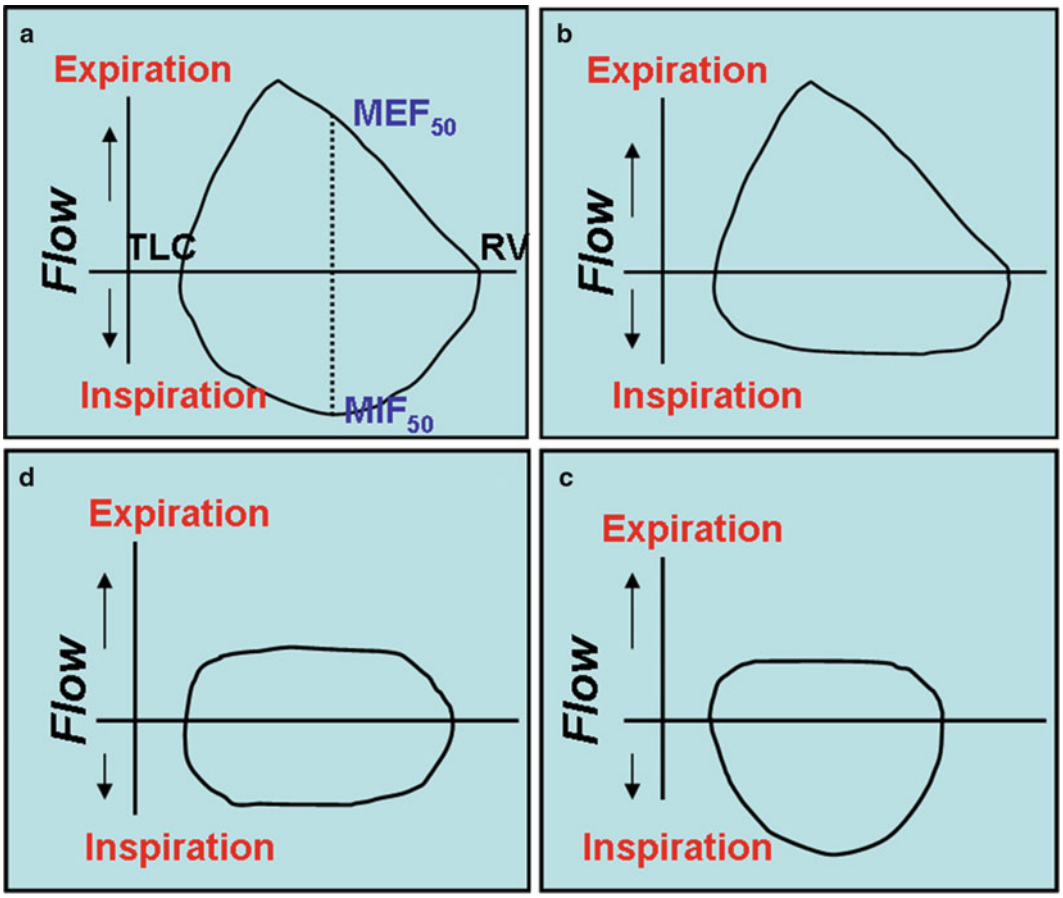

Fig. 7.2 Flow-volume loops. (**a**), normal. (**b**), variable extrathoracic obstruction. (**c**), variable intrathoracic obstruction. (**d**), fixed airflow obstruction

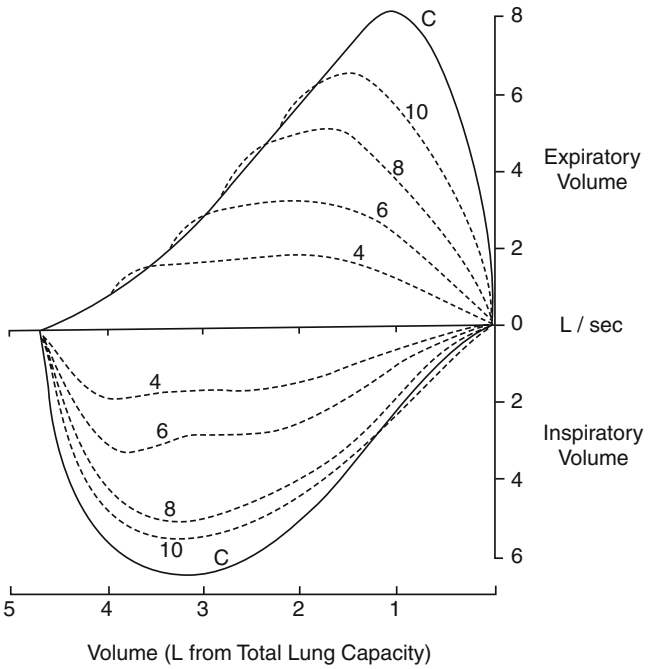

Fig. 7.3 Flow-volume loops obtained from breathing through progressively smaller orifices

pleural pressure which becomes more negative during inspiration helping to keep these airways open. Thus, obstruction within the extrathoracic airway will impact on flow to a greater extent during inspiration (Fig. 7.2b, variable extrathoracic obstruction), whereas obstruction within the intrathoracic airway will affect flow more during expiration when the transmural airway pressure increases and these airways are tending to collapse (Fig. 7.2c, variable intrathoracic obstruction). If the obstruction is stiff or circumferential, these dynamic changes do not impact on the flow as it is limited throughout the cycle and this can be seen as plateauing of both the inspiratory and expiratory limbs of the flow-volume loop (Fig. 7.2d, fixed obstruction). Where there is unilateral main bronchus obstruction, the maximum inspiratory flow tends to be higher at the beginning than towards the end of the forced inspiration because of a delay in gas filling.

Since these original observations by Miller and Hyatt, a number of other criteria based on visual inspection of the flow-volume loop have been proposed as useful although non-specific for the detection of upper airway obstruction. These include biphasic shape and oscillations in the expiratory or inspiratory curves (Table 7.1).

Table 7.1 Proposed criteria for distinguishing *upper airway obstruction* on pulmonary function tests

Visual criteria reported by	Reported by
Presence of a plateau	Miller and Hyatt 1969
Biphasic shape	
Presence of oscillations	
Quantitative	
Increased PEFR:PIFR	Nairn 1963
Increased MEF50 to MIP50	Jordanoglou and Pride 1968
FIF 50% ≤ 100 L/min	Rotman 1975
FEF 50%/FIF 50% ≥ 1	Rotman 1975
FIF25-75/FEF25-75 <1	Owens 1983
FEV1/PEFR ≥ 10 ml/l/min – the peak flow is proportionately more reduced by upper airway obstruction than is the FEV1	Empey 1972; Rotman 1975
FEV1/FEV0.5 ≥ 1.5 – the FEV0.5 is proportionately more reduced by upper airway obstruction than the FEV1	Yernault 1973; Rotman 1975
DLCO single breath unchanged	Sackner 1972

MIP50 maximal inspiratory flow at 50% of the vital capacity, *FIF50%* forced inspiratory flow at 50% of the vital capacity, *FEF50%* forced expiratory flow at 50% of the vital capacity, *PEFR* peak expiratory flow rate measured in litres per minute, *FEV1* forced expiratory volume in 1 s measured in millilitres, *FEV0.5* forced expiratory volume in ½ s measured in millilitres

Spirometry

Central airway obstruction primarily affects airflow by worsening airway resistance. Consequently, spirometry, which is a simple plot of expiratory volume against time, might be expected to be useful in detection. This was first proposed by Jordanoglou and Pride in 1968, and their observations were extended by Empey in 1972. While the FEV1 alone is an insensitive marker, a number of ratios of flow and other quantitative criteria have been investigated over the years and have been found useful in discriminating patients with airway obstruction proximal to the level of the carina. These quantitative criteria are outlined in Table 7.1.

The essential finding from these studies is that the cardinal feature of upper airway obstruction is a reduction in flow at large lung volumes, whether inspiratory or expiratory. This is a consequence of the fact that at large lung volumes, flow is effort-dependent, whereas at low lung volumes, the intrathoracic airways are compressed and flow becomes dependent on lung elastic recoil which is effort independent. This becomes useful in the discrimination of small airway obstruction (COPD) from upper airway obstruction.

It is important to be aware when interpreting the spirometry and flow-volume loops that patient effort has a major impact on all these ratios, and so it is crucial that the patient effort is as near maximal as possible, particularly during inspiration. Poor inspiratory effort is common and when isolated rarely indicates upper airway obstruction, and the technician should confirm the quality of the test and effort on the report.

Total Lung Volumes/Diffusion Capacity

In the absence of coexisting peripheral airway obstruction, asthma or other pathology, the overall lung volumes as measured by nitrogen washout or plethysmography should be normal in fixed airway obstruction as is the single breath diffusion capacity of carbon monoxide. However, these tests are often difficult for the patient with central airway obstruction to perform.

Effect of Exercise and Posture

In central airway obstruction, airflow turbulence and airway resistance increase with higher respiratory rates. The maximal voluntary ventilation (MVV) manoeuvre can therefore bring out unsuspected airway obstruction because as the respiratory rate rises, there is fall in exercise capacity due to hypoventilation associated with the climbing airway resistance and this leads to a large fall in observed MVV. A ratio of maximal voluntary ventilation to forced expiratory volume in 1 s of less than 25 is usually observed. Similar changes are seen with exercise, and thus, patients with fixed obstruction will often first complain of dyspnoea or stridor on exertion.

Alterations in the contour of the flow-volume loop can also occur with changes in posture, with the decreases in normal values seen in recumbency in normal subjects exacerbated in the setting of upper airway obstruction. Obtaining flow-volume loops in lying and standing positions may therefore increase the sensitivity of this method in detecting an upper airway lesion.

Fixed Airway Obstruction and COPD

Detection of concomitant upper airway lesions in patients with COPD may pose a particular challenge to the clinician as symptoms of progressive airway obstruction such as dyspnoea and wheeze may be common to COPD and can be missed. The expiratory limb of the flow-volume loop takes on a characteristic coved-out appearance in COPD due to loss of small airways and elastic recoil. As a consequence, the absence of a classic plateau in expiratory portion of the flow-volume loop does not rule out the presence of coexisting upper airway obstruction.

The FEV1 to FEV0.5 ratio has been proposed as a useful index for separation of the functional abnormalities seen in COPD from those of upper airway obstruction. When the FEV0.5 is less than 60% of the FEV1, a diagnosis of central airway obstruction is suggested. A further non-specific method of discrimination can be observed with inhalation of heliox. Heliox improves peak flow in the setting of turbulent airflow as seen in airway obstruction but has no impact on

the obstruction seen in COPD, which is a small airway disease in which flow is predominantly laminar.

The various indices from the flow-volume loop and spirogram that have been found useful in distinguishing upper airway obstruction and COPD are given in Table 7.1.

Interpretation of PFTS

While the changes in visual and quantitative findings on spirometry or flow-volume loop delineated in Table 7.1 are well described, most of the observations and original studies on which they are based were carried out in normal subjects or in patients breathing through a mouthpiece where airflow obstruction was simulated. This should be borne in mind as the diagnostic performance of the criteria outlined in detecting central airway obstruction is uncertain, and in fact to date, there is a dearth of published data evaluating this. A recent paper from Modrykamien and colleagues from the Cleveland Clinic evaluating performance of these criteria in consecutive patients undergoing pulmonary function suggested a presence of central airway obstruction of 7.5%. However, the criteria performed poorly alone, and while there was an increased sensitivity when an aggregate performance scale was used, overall sensitivity of these physiological tests was less than 70%.

While this suggests better criteria to help predict the presence of upper airway obstruction may be established, for now, it underlines how essential further evaluation with airway inspection by bronchoscopy and imaging is in the assessment of suspected central airway obstruction.

Clinical

Presentation

Chronic upper airway obstruction may progress insidiously and as a result goes unrecognised and often misdiagnosed, often masquerading for years as asthma or chronic obstructive pulmonary disease. Figures 7.4, 7.5, 7.6, and 7.7 provide case examples with classic flow-volume loops showing fixed airway obstruction. With anatomically fixed obstruction, wheezing and dyspnoea are typically unresponsive to bronchodilators, and failure of a patient to improve with these treatments should prompt further evaluation.

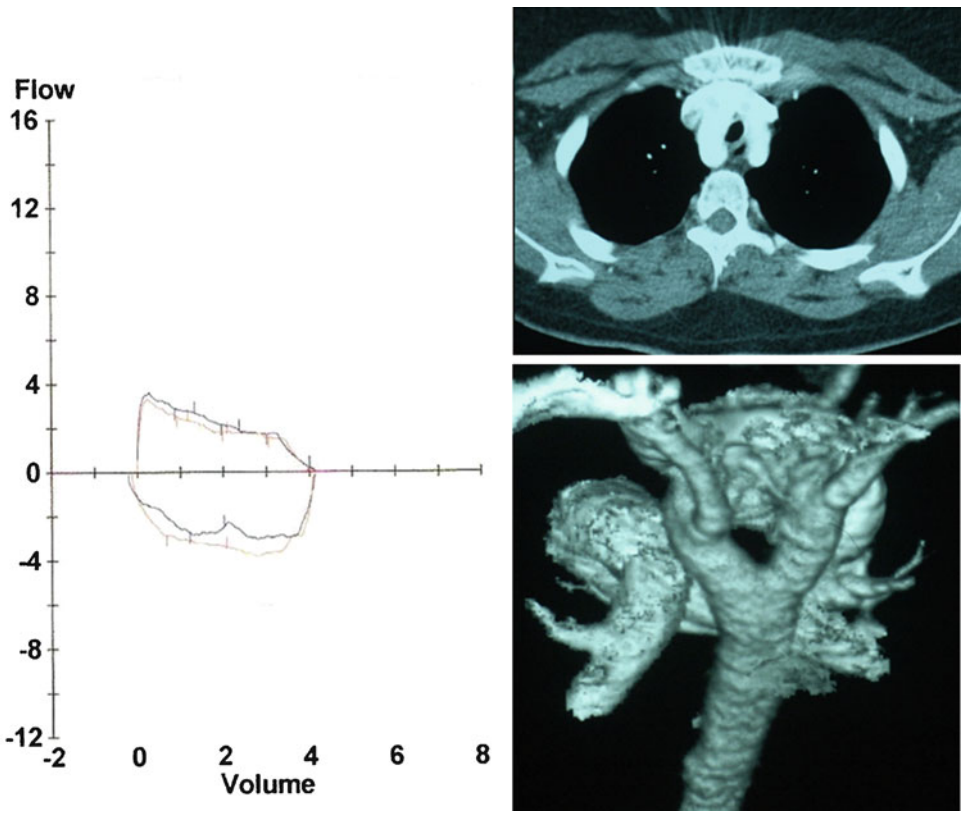

Fig. 7.4 A 16-year-old girl presented with a 6-year history of wheeze. The flow-volume loop shows characteristic plateau in inspiratory and expiratory limbs, suggesting fixed airway obstruction. A thoracic CT angiogram was performed (images courtesy of Dr. Sanjay Chotirmall) and shows a vascular ring with dual aortic arch and ascending aorta bifurcation anterior to the mid-trachea causing compression

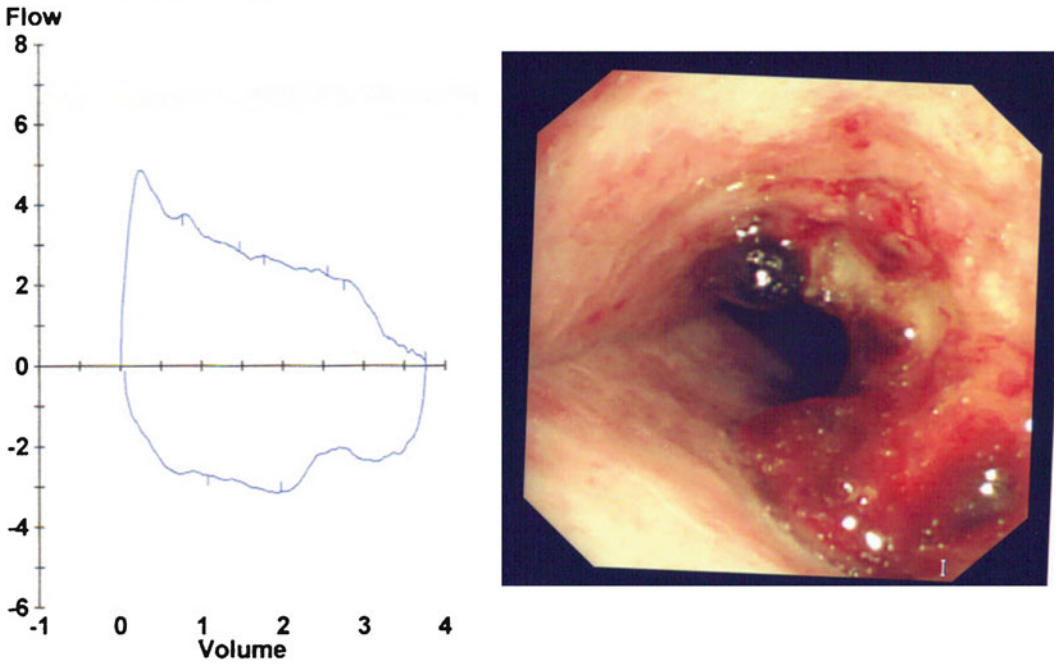

Fig. 7.5 A 65-year-old man with a history of locally advanced oesophageal cancer presented with exertional dyspnoea and stridor. Flow-volume loop and bronchoscopic view of his trachea are shown. There is fixed airway obstruction with tumour arising from the anterior and right tracheal wall. Biopsies confirmed metastatic oesophageal cancer, and the patient underwent airway debridement and stenting followed by radiotherapy

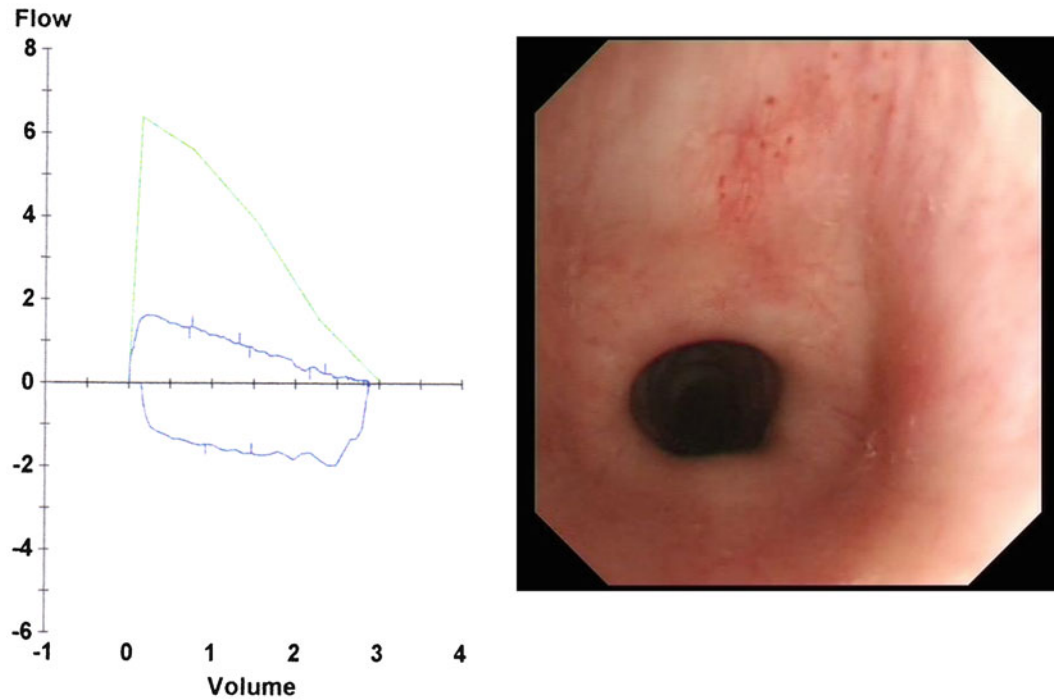

Fig 7.6 A 53-year-old woman with a history of relapsing polychondritis presents with exertional dyspnoea and stridor. The flow-volume loop demonstrates classical fixed airway obstruction, and bronchoscopic view shows a trapped first tracheal ring

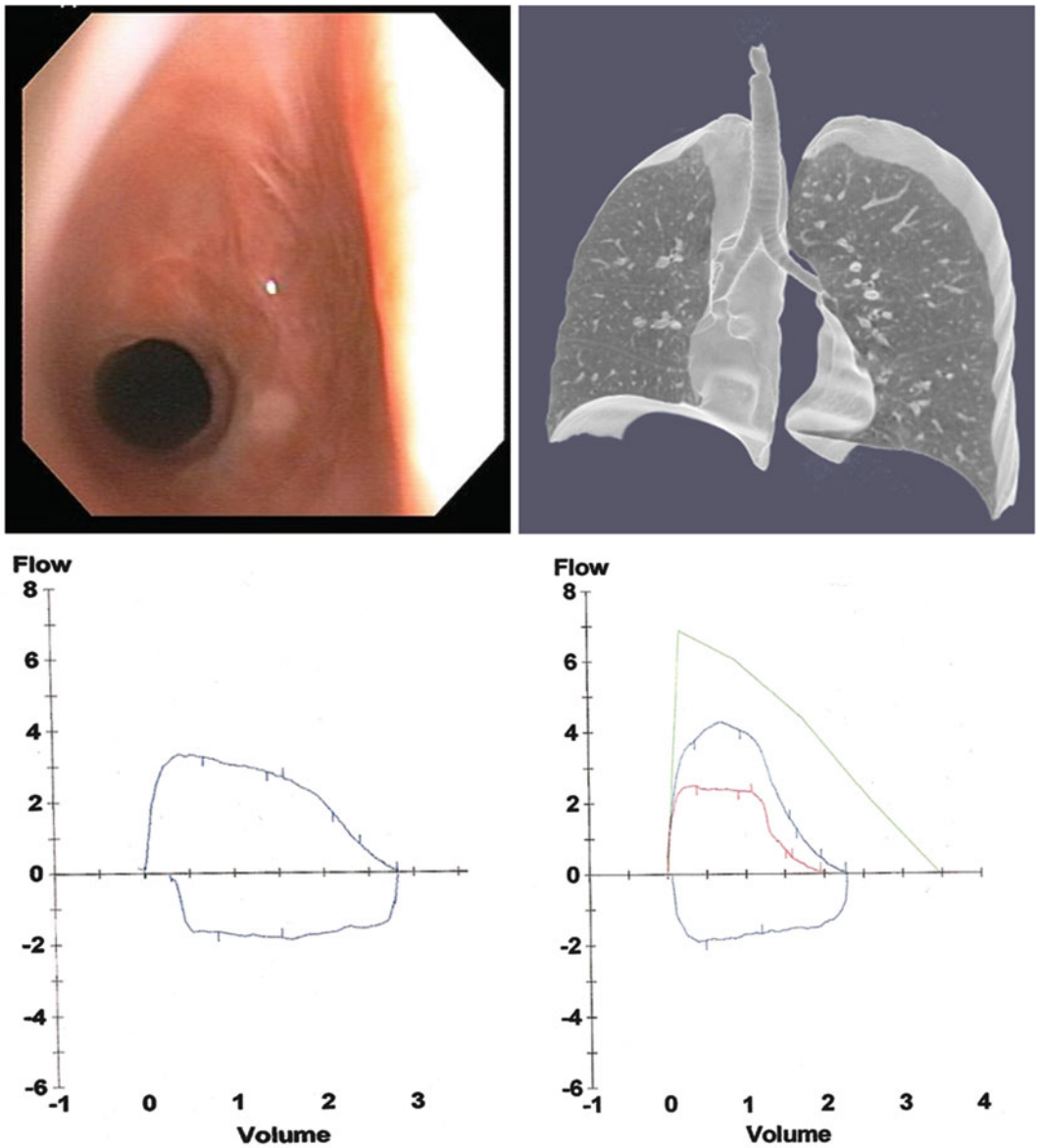

Fig. 7.7 A 31-year-old woman presents with idiopathic subglottic stricture. The *upper* airway bronchoscopic image and CT reconstruction above shows short segment of circumferential tracheal stenosis. On the *bottom*, the flow-volume loops before (*left*) and 6 weeks after bronchoscopic dilatation showing improvement in expiratory limb of the curve

Dyspnoea is the usual presenting symptom and may be worse on lying flat as well as with exercise. Typically, exertional dyspnoea occurs when the airway luminal diameter is reduced to about 8 mm. In patients with a laryngeal level of obstruction, dysphonia may also be a feature. Resting dyspnoea does not usually result until the airway diameter falls to 5 mm, at which point on examination stridor is the cardinal feature. Stridor can be defined as an abnormal, high-pitched sound which results from turbulent airflow through a partially obstructed upper airway. It is heard best when the airflow is maximal, that is, with a deep breath and at the level where the airway lumen decreases, for example, over the neck. The tone of stridor varies, and it can be variously described as harsh, musical or breathy. It should be easy clinically to differentiate from stertor, which is heavy snoring-type inspiratory sound typically generated at the level of the naso- or oropharynx and not associated with airway disease.

Worsening stridor can be observed when minute ventilation increases, such as during exercise. Because the airway lumen can reduce so dramatically before symptoms intervene, over half of patients with fixed airway obstruction will present with respiratory distress. Frequently, this is precipitated by an upper respiratory tract infection which causes increase work of breathing and further airway lumen compromise.

Table 7.2 Causes of fixed large airway obstruction

Non-malignant	Tumours
• Extrinsic	• Benign tracheal tumours
Goitre	Haemangiomas
Lymphadenopathy	Granular cell tumours
Vascular compression	Papillomatosis
	Lipoma
• Post-intubation stenosis	Pleomorphic adenoma
• Idiopathic	Chondroma
• Infection	Neurofibroma
Tuberculosis	
Histoplasmosis	
Mucormycosis	
Nocardia	• Malignant
	Bronchogenic carcinoma
	Adenoid cystic carcinoma
	Mucoepidermoid carcinoma
	Angiosarcoma
	Carcinoid tumours
	Kaposi's sarcoma
• Granulation tissue, e.g. anastomotic	• Metastatic disease to airway
• Inflammatory/infiltrative	Lung
Amyloid	Renal
Sarcoidosis	Breast
Relapsing polychondritis	Thyroid
Wegeners	Colon
• Foreign bodies	Melanoma
• Iatrogenic	
• Tracheobronchopathia osteoplastica	

Etiology

There are a multitude of causes of fixed upper airway obstruction, and these are listed in Table 7.2. Outside of malignant airway disease, a common and growing cause of fixed airway obstruction is previous intubation and tracheostomy. The incidence of all types of injury to the larynx after endotracheal intubation in the past ranged from 60% to 94%, and significant tracheal stenosis occurred in up to 1 in 5 cases in the past. This has thankfully been reduced in the last decade with the use of low-pressure, high-volume cuffs and the increase in use of tracheostomy where endotracheal intubation for longer than 2 weeks is required. Factors that have been found to increase the risk of laryngeal injury include laryngeal trauma during extubation, large endotracheal tube calibre, oral intubation, severe respiratory failure, diabetes and female gender. The incidence of tracheal stenosis following tracheotomy varies, and it can occur at the site of the stoma, cuff or tip. Severe stenosis requiring surgical intervention probably occurs in less than 5% of patients.

Diagnosis

A complete history and physical is essential in the evaluation of the patient with suspected fixed airway obstruction, and lung function studies, as has been highlighted in this chapter, can be extremely useful. However, endoscopy with either rigid or flexible bronchscope and additional imaging studies with computerised tomography (CT) of the neck, trachea and thorax are usually required to further define the cause. Other reported useful imaging adjuncts in assessment of level and severity of obstruction include spiral CT, virtual bronchoscopy with multiplanar reformatting, morphometric bronchoscopy and magnetic resonance imaging (MRI). MRI is the preferred modality in evaluating paratracheal masses in patients who have allergy to iodinated contrast material used for CT scans and, because it does not involve ionising radiation, may also be useful for evaluating paratracheal abnormalities in children. Endobronchial ultrasound (EBUS), in particular the radial probe device, has a particular role in that it has been found to be more sensitive than CT in distinguishing tissue invasion from external compression of the airway. The 20-MHz frequency of this probe providing a resolution of less than 1 mm and the high level of structural detail of the airway wall that is provided can be instructive in treatment planning.

Summary

Fixed airway obstruction can be defined physiologically as obstruction that persists throughout the respiratory cycle. It should be suspected in any patient with upper airway symptoms of wheeze, stridor or exertional dyspnoea in particular where these symptoms have been unresponsive to conventional therapy or where a history of tracheal intubation exists. Symptoms result from turbulent airflow around the site of obstruction causing increased airway resistance. Pulmonary function testing, especially visual inspection of the flow-volume loop, remains an effective way of detecting upper airway obstruction. Plateauing or flattening of both the inspiratory and expiratory limbs during flow-volume measurement is the hallmark of fixed obstruction. Where only one limb is flattened, this suggests that the obstruction is variable in nature. Upper airway obstruction should not be confused with airflow obstruction that occurs in chronic obstructive pulmonary disease or asthma, conditions which affect smaller airways and can be discriminated from upper airway obstruction by careful examination of the flow-volume loop where characteristic patterns can be seen. Where upper airway obstruction and obstructive airway disease coexist, a number of quantitative criteria have been proposed based on pulmonary function to discriminate.

While the flow-volume loop and spirometry are useful in detecting fixed airway obstruction and are cheap, readily available and generally easy to perform, testing is volitional in nature, and it is therefore important that the technician records the patient effort, in particular during the inspiratory cycle which is often performed poorly. Overall, while very informative, tests of pulmonary function lack sufficient sensitivity for upper airway obstruction, and where suspected clinically, further assessment by bronchoscopy and airway imaging is necessary.

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Airway Imaging

8

Claus P. Heussel

Computed Tomography

Since multislice CT scanners (MSCT), which are able to scan the whole lung in thin sections (<0.5 mm) within a single breath hold, are widely available, CT has become a new role in imaging of the tracheobronchial tree. Three-dimensional, time-resolved, and four-dimensional visualization as well as quantitative analysis became possible by fast scanners with higher resolution in z-axis. Many of these multidimensional visualizations have to be experienced interactively at the workstation or at least reviewed as an animated movie (Figs. 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, and 8.7). This cannot be demonstrated in this two-dimensional book and is therefore displayed limitedly.

While transversal CT images are frequently sufficient for evaluating many of the airway abnormalities, there are several limitations that should lead to further postprocessing:

- Inadequate representation of airways oriented obliquely to the axial plane
- Short and subtle stenoses (Figs. 8.1, 8.3, and 8.6)
- Underestimation of the three-dimensional extent of disease and therefore
- Limited possibility to visualize the complex three-dimensional relationship of the disease to airways and adjacent mediastinal structures
- Impossibility to display the surfaces and therefore stenosis of airways that lie parallel to the transversal plane (Figs. 8.1 and 8.8)

Due to the need of thin-section volumetric CT, a large number of images containing hundreds of images are generated. As a consequence, the use of retrospectively reconstructed 2D and 3D images should be considered routinely in preparation of bronchoscopy. MSCT starts with a reconstruction of these two-dimensional images, which can be reformatted in further dimensions. Adequate imaging of the airways to be reformatted, visualizing down to a segmental level requires a maximal slice thickness of 1 mm or below. If thinner slices and/or larger overlap are available (typically 0.5–0.75 mm, 50% overlap), especially small lesions, thin stenosis and oblique structure are significantly better visualized after reformat. These thin sections require substantial storage capacity at the scanner, at the postprocessing workstation, and at the PACS (picture archiving computer system). However, they are essential for adequate postprocessing (30 cm long, 0.75-mm slice thickness, 50% overlap $\Rightarrow$ 600 images $\Rightarrow$ 300 MB). Fast data acquisition is also essential in imaging of the airways since many patients suffer from dyspnea. Severe artifacts as a result of continuous respiration cut the diagnostic quality impressively and occur in secondary reformats (Fig. 8.4d).

The usage of nonenhanced low-dose technique (e.g., 70mAs as in Fig. 8.1) is sufficient to evaluate the central airways and the peripheral airways as well if three-dimensional

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A. Ernst and F.J.F. Herth (eds.), *Principles and Practice of Interventional Pulmonology*,
DOI 10.1007/978-1-4614-4292-9_8,

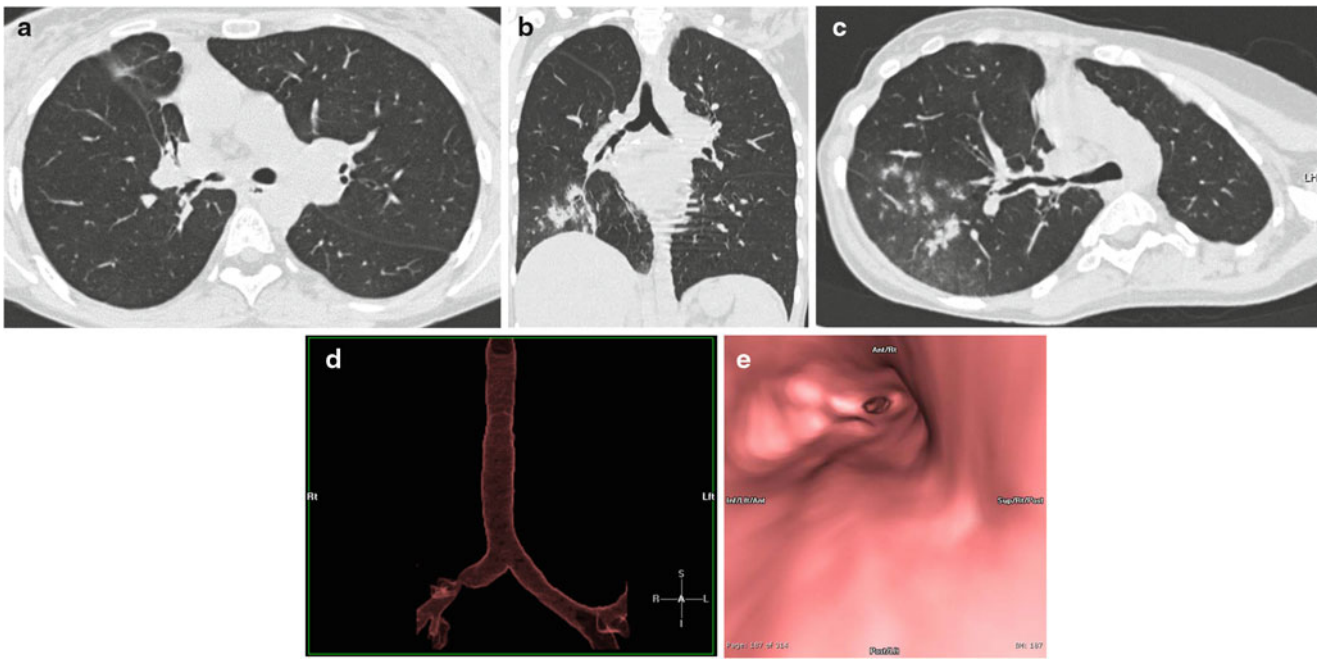

Fig. 8.1 Nonenhanced thin-section CT scan of a 26-year-old female who underwent bilateral lung transplantation 6 months before due to cystic fibrosis. She went to hospital due to recurrent fever, emesis with some nonproductive cough, and global deterioration. FEV_1 was 2.3l (71%). CMV pp65 antigenemia was mild positive (260 IU/ml). Bronchopneumonic infiltration was evident on CT in the *right lower lobe* (B+C) as well as the causal stenosis of the *right* main stem bronchus (**a**). Multiplanar reformat and postprocessing helped to identify the stenosis and to quantify its severity and extent (**b**, **c**, **d**). Virtual bronchoscopy was calculated for demonstration purposes and matches well with real bronchoscopic view. Biopsy was taken to differentiate between graft rejection and infection (the latter was the reason). (**a**) Transversal CT scan, (**b**) coronal reformat, (**c**) paracoronal reformat (single oblique), (**d**) surface-shaded rendering, (**e**) virtual bronchoscopy

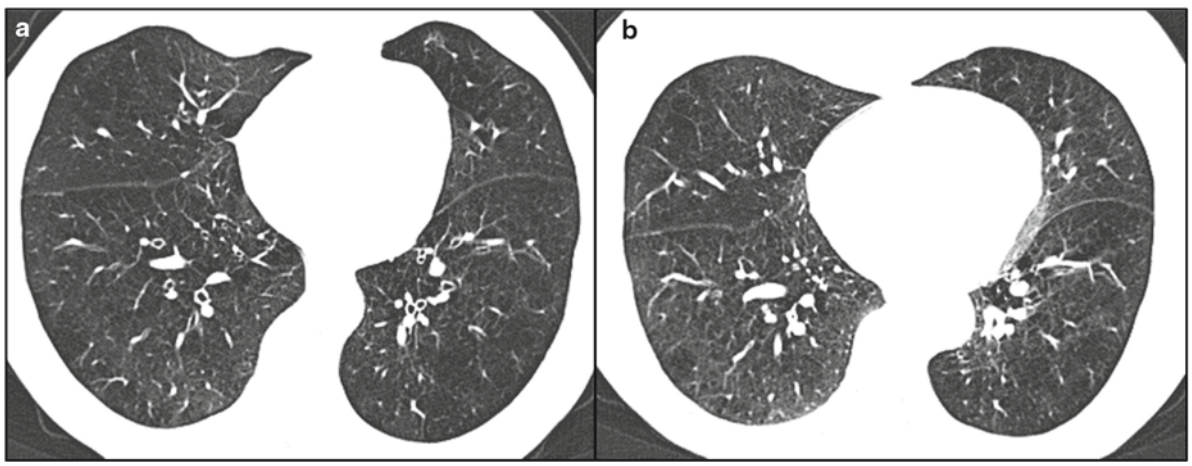

Fig. 8.2 The 57-year-old patient acquired 30 pack years and suffered from COPD IV°. She was planned for interventional emphysema therapy and therefore underwent paired inspiratory (**a**) and expiratory (**b**) thin-section CT scan. A special window-level setting (width 1,000 HU, level – 800 HU) demonstrated the inhomogeneous density of the lung parenchyma in both breath holds (**a**+**b**), especially in the expiratory one (**b**). There are subsegmental regions with adequate increase after expiration (*right lower lobe*), representing a relative increase of tissue per voxel. In contrast, other subsegmental areas did not change their density in expiration (*left lower lobe*), indicating air trapping as an indirect sign of obstructive small airway disease. Besides the indirect signs, also direct collapse of the segmental airways is visible in this image pair: All segmental bronchi are open at inspiratory CT (**a**), while almost all airways appear to be collapsed at the expiratory scan (**b**)

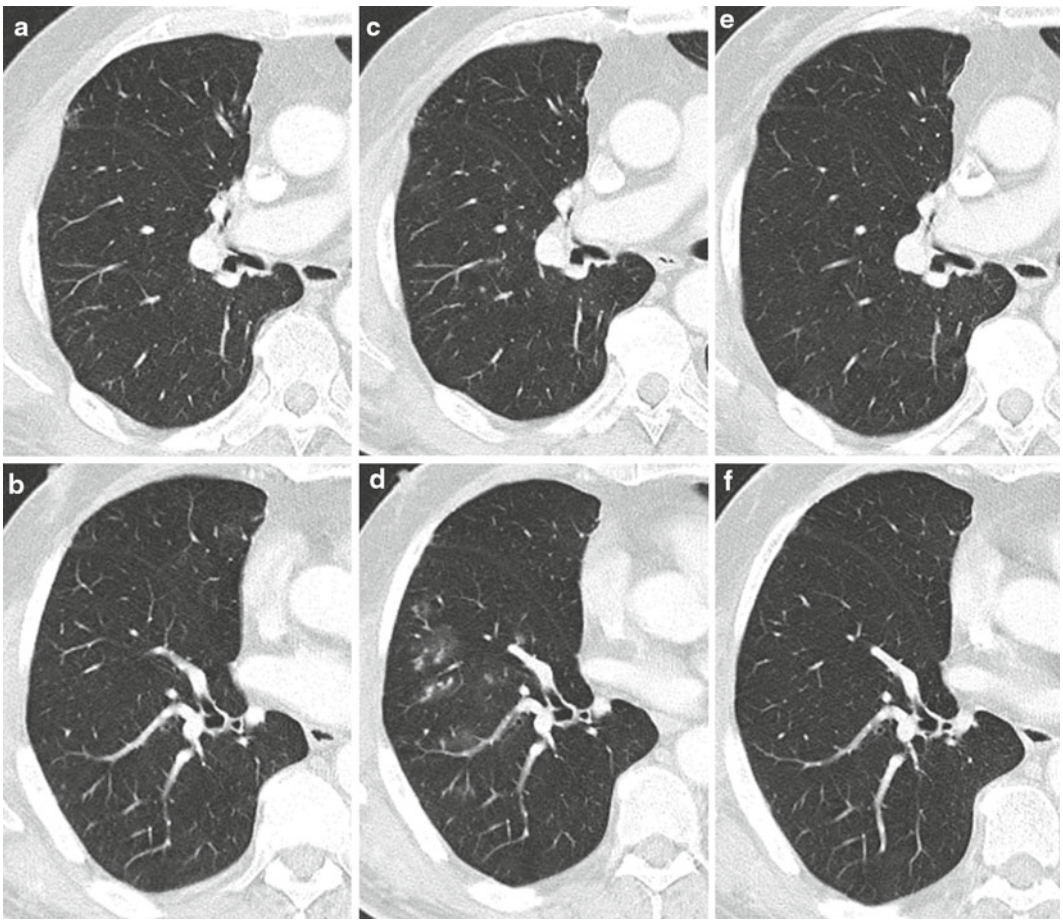

Fig. 8.3 (**a**+**b**) Prescan, (**c**+**d**) presentation, and (**e**+**f**) 6 months later, (**a**+**c**+**e**) at an *lower* lobe segmental ramification level. (**b**+**d**+**f**) Bronchus intermedius level. The 70-year-old patient was *upper* lobectomized *right* 4 years before due to stage I non-small-cell lung cancer and reported cough and bronchial infection since some weeks. The CT scan (**c**+**d**) demonstrated focal ill-defined nodules in the *right lower lobe* (**c**), which were newly developed as compared to the prescan (**b**). While analyzing the feeding bronchi, a bronchial kinking was evident in *middle* and *right lower lobes*. Together with the evident clinical symptoms, this was rated as bronchopneumonia, while pulmonary metastases were considered unlikely. The findings disappeared at the routine follow-up (**e**+**f**), indicating the infection to be treated successfully

reformats are intended. Also, emphysema quantification requires nonenhanced scans; intravenous contrast enhancement might be used if additional questions are to be answered (e.g., pulmonary embolism, relationship to a tumor or vessel). Additional acquisitions paired inspiratory and expiratory breath hold, cine-CT [,] or in prone position can help to evaluate airway stability (bronchial collapse) and air trapping as a sign of obstructive small airway disease (Figs. 8.2 and 8.5).

Multiplanar Reformation

Besides cross-sectional postprocessing with multiplanar reformats, surface-shaded techniques are helpful to display the tracheobronchial tree from inside. Virtual bronchoscopy (VB) as an artificial substitute to real bronchoscopy (RB) allows for similar inspection of the central airways. In contrast to real bronchoscopy, the user can pass an obstructing lesion, accurately measure its

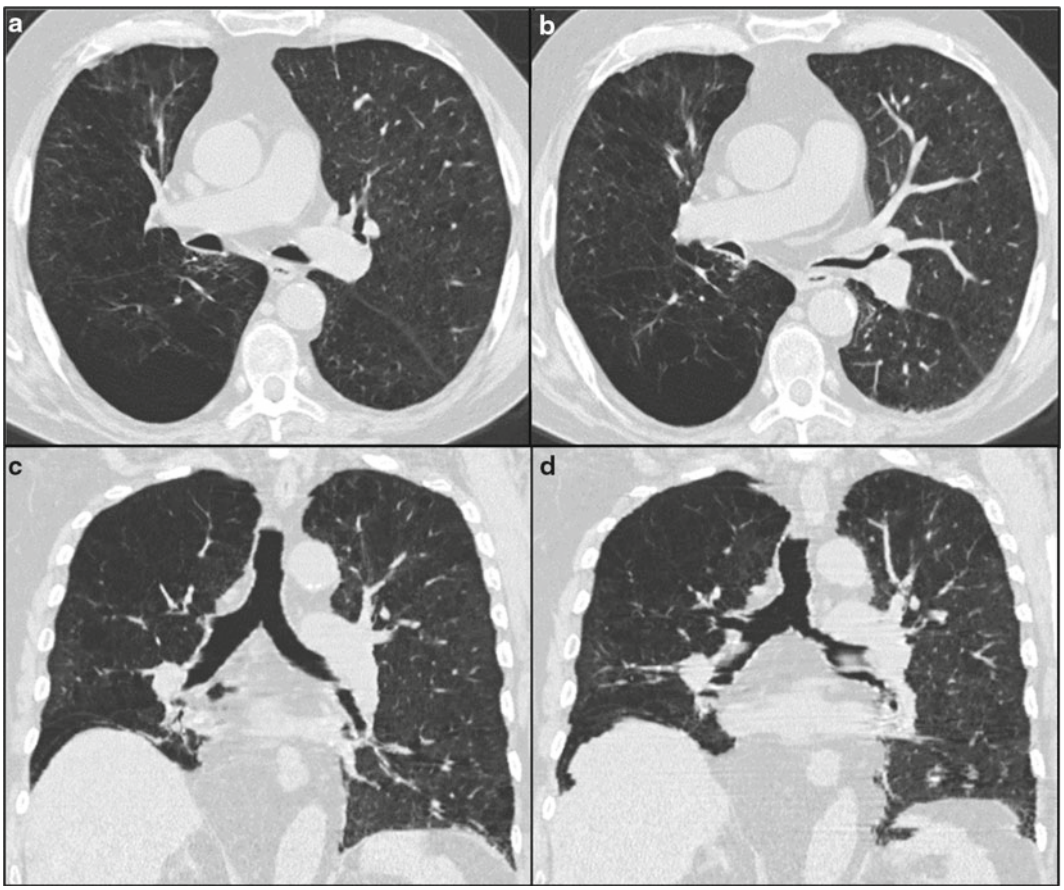

Fig. 8.4 The 81-year-old patient acquired 40 pack years and suffered from COPD III. He was planned for interventional emphysema therapy and therefore underwent paired inspiratory (**a**+**c**) and expiratory (**b**+**d**) thin-section CT scan. The comparison of the mainstem bronchi at inspiratory and expiratory CT indicates a relevant luminal change. The coronal reformat of the expiratory scan shows severe staring artifacts due to respiratory effect (**d**): Expiratory breath holding requires more compliance and pulmonary reserve as compared to inspiratory breath holding and is therefore frequently limited in patients suffering from severe lung disease. In this clinical scenario, fast CT scanning is relevant in particular since respiration artifacts occur in the expiratory scan (**d**). (**a**) Inspiratory breath hold, (**b**) expiratory breath hold, (**c**) coronal reformat of inspiratory breath hold, (**d**) coronal reformat of expiratory breath hold

dimension, and turn round the virtual bronchoscope to take a look from each direction onto a lesion, including backward from distal to proximal. Also, the time effort is limited by neither patient nor anesthesia. However, color coding in VR is artificial and might be misleading (e.g., mucus might appear as soft tissue), spatial resolution is worse, and the interventional manipulative options of RB are missing. Thus, VB is mainly complementary to bronchoscopy in the assessment of patients with suspicion of airway stenosis. To get advantages of both techniques, CT should be done prior to bronchoscopy as a navigation system. This provides valuable information, e.g., whether the airway is obstructed by extrinsic compression, intraluminal disease, or an intrinsic airway disease. Also, the relationship of the airway to the adjacent anatomy is displayed by cross-sectional imaging. CT is therefore essential in decision whether the patient is a candidate for surgical resection, radiation therapy, or interventional treatment. If airway stenting is planned, CT findings can help to determine the type, size, and length of the individually appropriate stent. Then, several techniques are available to merge computer-assisted VR and RB in real time.

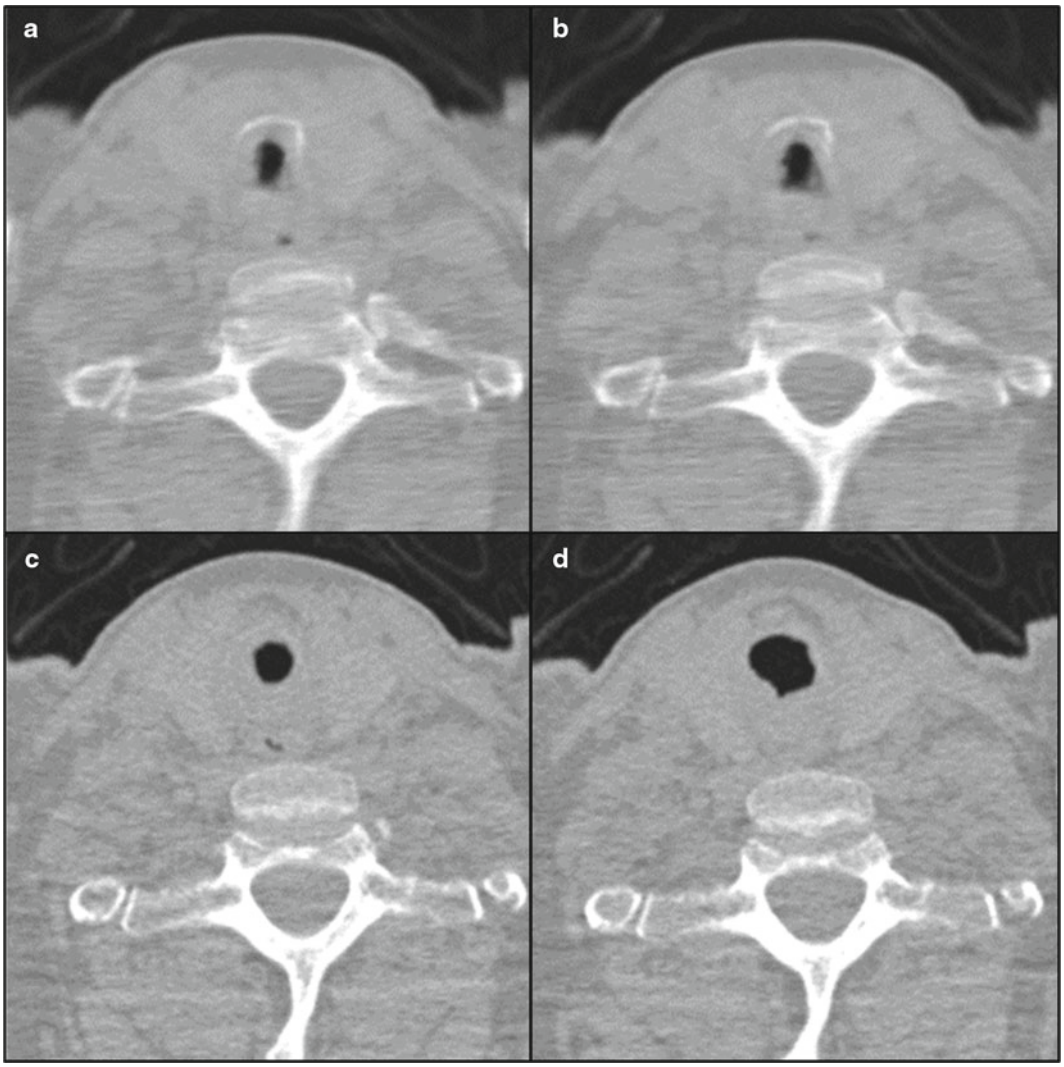

Fig. 8.5 (**a**) inspiratory breath hold, (**b**) expiratory breath hold, (**c**) maximal lumen in cine-CT, (**d**) expiratory breath hold. The 67-year-old patient was tracheotomized after substitution of mitral valve due to postoperative complications including seizure and pneumonia 2 months ago. Paired inspiratory and expiratory CT showed stenosis of the trachea at the level of tracheotomy (**a**+**b**). Cine-CT acquired during continuous respiration demonstrated additionally a relevant collapse at this level (**c**+**d**). Thus, an end-to-end resection of 3.5-cm trachea was performed

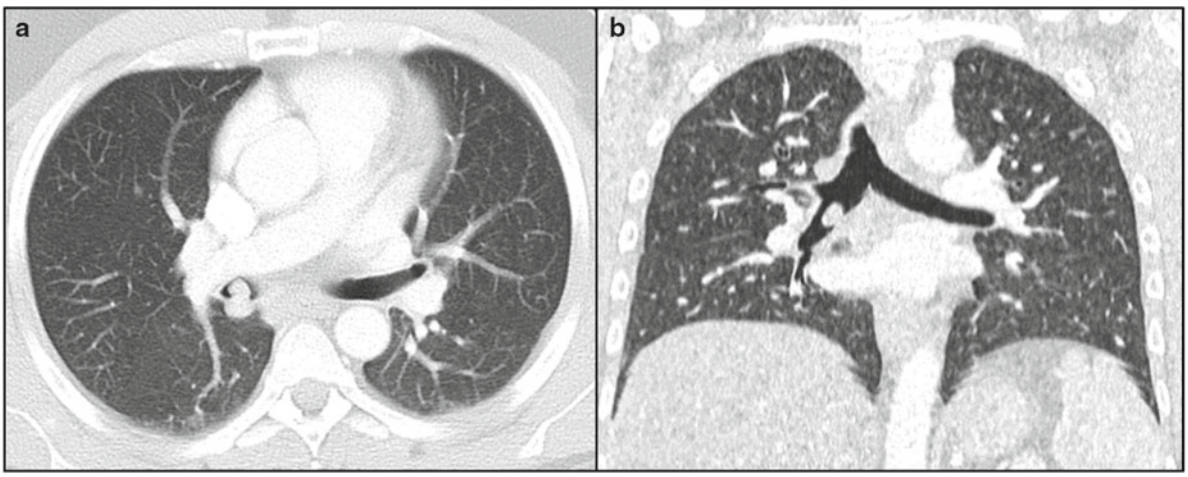

Fig. 8.6 (**a**) transversal CT, (**b**) coronal reformat. The 37-year-old male patient presented with hemoptysis. CT revealed polypoid mass in the bronchus intermedius (**a**+**b**), which was identified as typical carcinoid using bronchoscopy. Circular segmental resection of the bronchus intermedius was performed

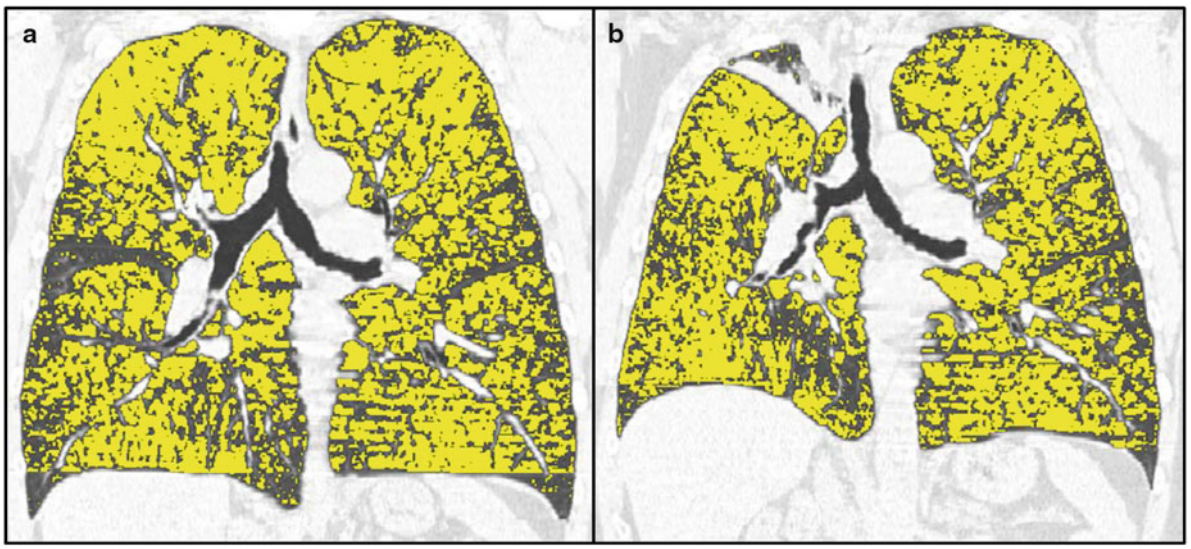

Fig. 8.7 The 61-year-old male patient acquired 60 pack years and presented COPD IV (FEV1 0.5 l, 6-min walk test 150 m). CT revealed severe diffuse bilateral centrilobular emphysema (emphysema index 48%, 15th percentile -983HU). After endobronchial placement of three valves in the *right upper lobe*, subtotal upper lobe atelectasis was observed and analysis improved to FEV1 0.8 l (25%), 6-min walk test 200 m, emphysema index 46%, and 15th percentile -981HU. (**a**) Prescan, (**b**) post valve implantation

Interventional Lung Volume Reduction

Besides conservative treatment of patients suffering from severe emphysema and lung transplantation, a variety of surgical and interventional strategies are established and under investigation to improve the function of residual lung parenchyma. The main mechanism is the interventional or surgical deflation of severely emphysematous destroyed lung parenchyma. Those procedures can either be reversible (device placement) or irreversible (i.e., glue or steam instillation or surgical resection). For adequate identification of the individual treatment strategy and optimal target identification, the extent and severity of disease as identified by CT has proved one of the most important predictors of a successful outcome (Fig. 8.7). Currently CT-based fissure analysis is paid attention to predict collateral ventilation and/or prediction of atelectasis. Besides the morphological information as derived by CT, regional functional data from V/Q scanning is applied here. In the future, CT perfusion mapping as well as MRI based perfusion and ventilation mapping will play a relevant role to identify the optimal target for regional emphysema treatment as well as for monitoring of lung disease in conservative therapies.

Bronchial Wall Quantification

In diffuse bronchial disease such as COPD or cystic fibrosis, the global quantification of bronchial wall thickness might serve as a surrogate parameter of the activity, e.g., of inflammation (Fig. 8.8). Therefore, several approaches have been introduced to measure the bronchial wall thickness at several localizations with or without computer assistance. Selection bias, spatial volume effect, and limited reproducibility are some of the limitations herein which can partially be overcome by a global quantification of all bronchial walls. This approach, however, is biased mainly by the assessment of bronchi for segmentation, which might be caused, e.g., by mucus impaction.

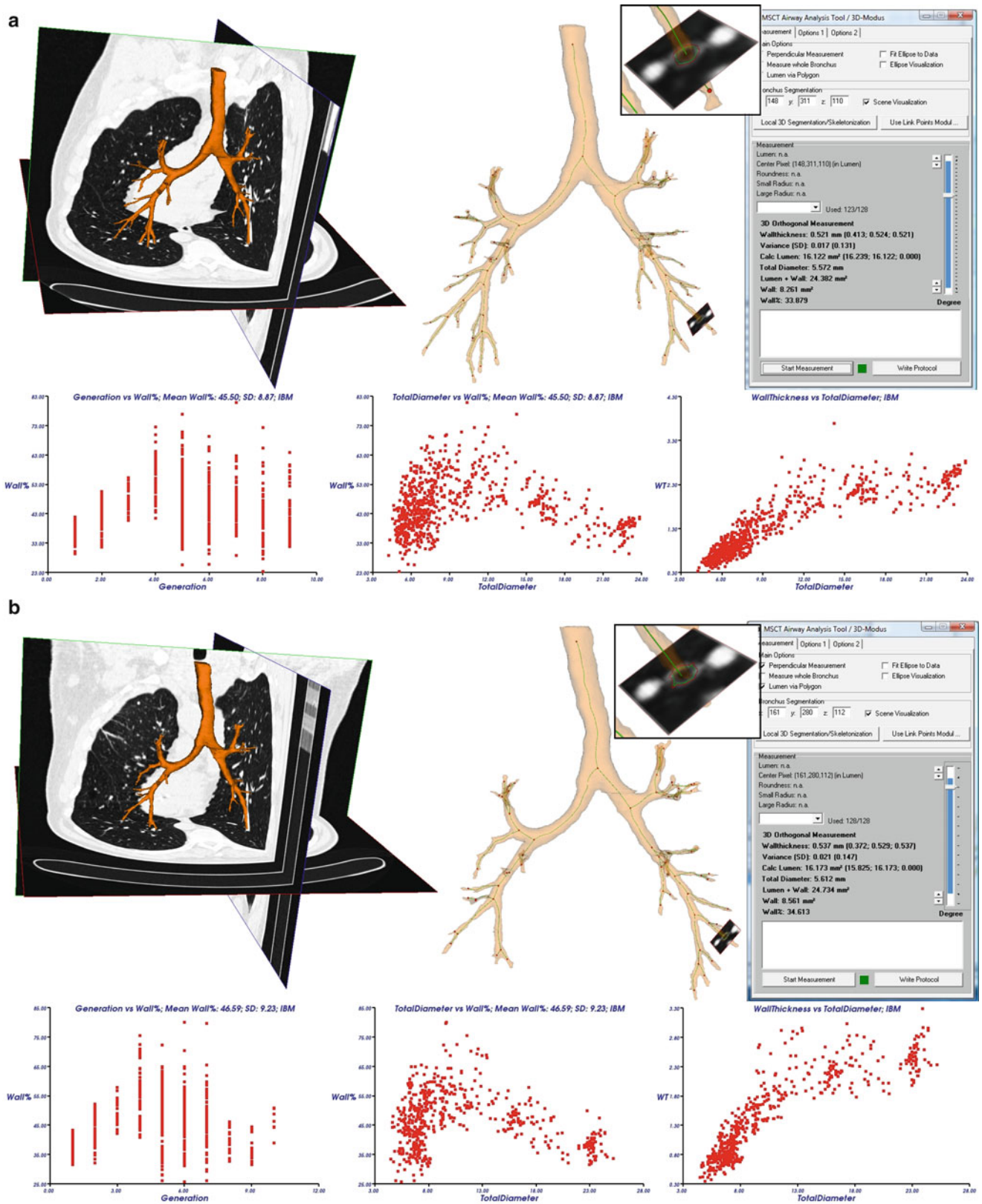

Fig. 8.8 The 68-year-old male patient presented with dyspnea. Global airway quantification from CT revealed a mean wall percentage of 45.5% in the baseline scan (mean wall thickness, 1.28) and a mean wall thickness of 46.6% in the follow-up scan (mean wall thickness, 1.43 mm). Thus, a relevant increase in the global bronchial wall thickness was measured. (**a**) Baseline, (**b**) 2-year follow-up

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Miss Melanie Segovic for the analysis of many CT data sets in adequate quality and the reliable data management together with Carola de Silva.

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Airway Anatomy

9

Arthur Sung

Introduction

Airway pathologies, both benign and malignant, have a myriad of clinical manifestations and radiologic findings; hence, expert knowledge and understanding of airway anatomy is a fundamental requirement to the practice of interventional pulmonology. To become competent in performing bronchoscopies entails proper training and dedicated practice, as well as accurate interpretation of endoscopic findings to incorporate into differential diagnosis and management strategies. Within the context of lung cancer, for example, bronchoscopies are routinely performed to acquire specimens from lymph nodes or airway lesions to establish histologic diagnosis. Precise localization of lesions can determine a patient's candidacy for surgical resection versus medical therapy. Consequently, airway anatomy details are vital to communications with other specialists in various disciplines, including thoracic surgeons, anethesiologists, and radiologists. For these reasons, it behooves those who perform airway procedures to be expert with respect to knowledge of airway anatomy.

The objective of this chapter is to provide both descriptive and applied anatomy of the upper and lower airways.

Upper Airway

Oral Cavity

The oral cavity consists of the teeth, tongue, and palates. The hard palate is a flat bony plate at the front of the roof of the mouth, whereas the soft palate is predominately muscular and terminates at the uvula. During deglutition, the soft palate displaces superiorly to assist with the closure of the nasopharynx. An overall assessment of the oral cavity should be performed prior to performing any type of procedures. Poor dental hygiene may be a risk factor for high-risk patients (e.g., alcohol abuse) with aspirations causing anaerobic infections and air-fluid cavities on imaging studies. The clinical examination should evaluate for the safety and contraindications for a procedure. A tooth that is mobile can become dislodged during manipulations and cause an airway obstruction. In a comatose or sedated patient, the tongue can frequently obstruct the upper airways and lead to oxygen desaturation and hypoventilation. During endotracheal intubation, the distal tip of the direct laryngoscope sweeps the tongue sideways in order to accommodate airway devices. Similarly, during rigid bronchoscopy intubation, the operator's nondominant hand should mobilize the tongue in order to allow passage of the rigid bronchoscope through the oropharynx. Clinical parameters used to assess for placement of artificial airways will be discussed later.

Nasal Anatomy

Nasal anatomy is complex; relevant structures include the nasal septum that divides the nose into two cavities and lateral nasal walls that are largely defined by the maxilla. Each of the walls is divided by three structures: the superior, middle, and inferior turbinates. When a bronchoscope is introduced through the nose, the inferior turbinate is seen laterally and the nasal septum is seen medially. When viewing the nasal cavity, the bronchoscopist should assess for septal deviation, hypertrophy of turbinates, presence of polyps, and the integrity of mucosa.

Oropharynx and Hypopharynx

The oropharynx lies beyond the base of the tongue and is bordered superiorly by the soft palate and extends to the tip of the epiglottis (Fig. 9.1). The palatine tonsils form the

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DOI 10.1007/978-1-4614-4292-9_9,

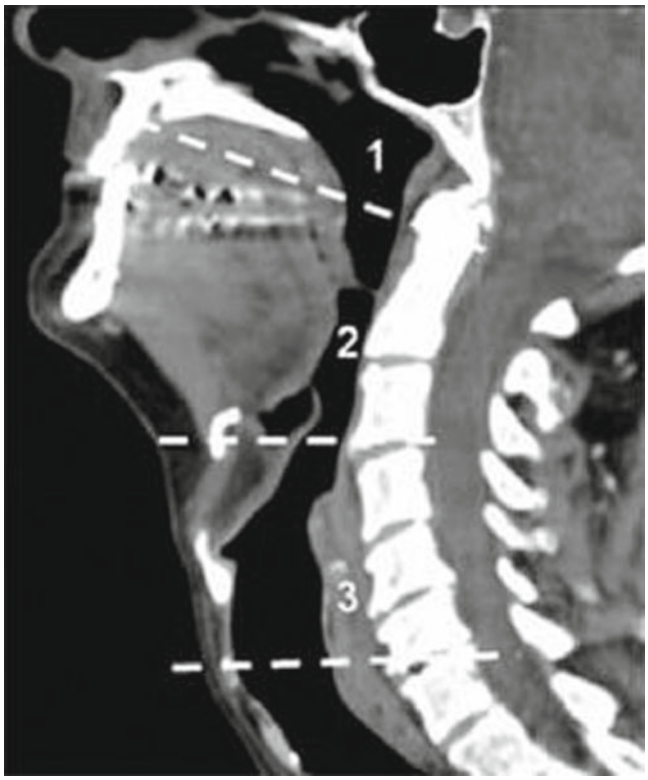

Fig. 9.1 Pharyngeal anatomy. Sagittal view of pharynx divided into (1) nasopharynx, (2) oropharynx, and (3) hypopharynx (From Nemec SF, Krestan CR, Noebauer-Huhmann IM, et al. Radiologische Normalanatomie des Larynx und Pharynx sowie bildgebende Techniken. Der Radiologe. 2009;49(1):8–16.) (Reprinted with kind permission from Springer Science+Business Media)

lateral walls on both sides. The space between the base of the tongue and the anterior surface of the epiglottis on either side constitutes the vallecula. The valleculae are separated by the median glossoepiglottic fold and bordered laterally on either side by the lateral glossoepiglottic folds. Valleculae are often locations for foreign-body entrapment and upper airway obstruction.

Examination of the oropharynx is a prerequisite to performing procedures of the airways. Commonly, the Mallampati classification is used to identify the amount of opening of the oropharynx. The open mouth is examined with the head in neutral position and the tongue protruded. The distance between the base of the tongue to the uvula, soft palate, and pharyngeal pillars is rated:

Class I: uvula, soft palate, and pharyngeal pillars are easily visible.

Class II: soft palate and pharyngeal pillars are visible.

Class III: soft palate alone is visible.

Class IV: only hard palate is visible.

In addition to examining the oropharynx, the opening of the mouth and thyromental distance (distance from the mandibular mentum to the superior thyroid notch during neck extension) should be assessed. A mouth opening of <2 finger widths and a thyromental distance <3 finger widths is suggestive of a difficult airway. A cooperative patient should be able to touch chin to chest, hyperextend the neck, and turn the head from side to side without pain or paresthesia. Cervicooccipital extension of less than a 160 ° angle at the hyoid bone limits proper positioning of the mouth and pharynx to visualize the glottis for endotracheal tube placement. A careful assessment of the mouth should also include evaluation for any prominent or protruding teeth which may block the view of the glottis. Although none of these parameters can singly predict a difficult airway, a careful overall assessment of the oral cavity is a prerequisite in the preparation of a procedure.

Hypopharynx

The hypopharynx lies inferior to the oropharnx. It is surrounded by three constrictor muscles and three inner longitudinal muscles that are responsible for swallowing. Traumatic intubations may lead to complications resulting in dysfunctional swallowing. This area, innervated by the glossopharyngeal and vagus nerves, contains the piriform recess, postcricoid region, and the posterior pharyngeal wall. The piriform recess is where the tip of the laryngoscope blade rests during intubation. The hypopharynx extends from the epiglottis to the level of cricoid cartilage, and then continues posterior to turn into the esophagus. During swallowing, the hypopharynx facilitates the food bolus into the upper digestive tract.

Larynx

The larynx is responsible for many functions such as phonation and respiration. The most important function, however, is to prevent aspirations.

Laryngeal Anatomy

The larynx is located at the level of the third to sixth cervical spine and inferior to the hyoid bone and superior to the trachea. In women and children, it is situated higher. The laryngeal apparatus is composed of mucosal folds, cartilages, muscles, and their respective neural innervations.

Mucosal Folds

The laryngeal mucosa is mostly lined with squamous and ciliated columnar epithelium. The vocal folds, posterior surface of the epiglottis, the aryepiglottic folds, and the posterior commissure are lined with squamous cell mucosa, while the rest of the laryngeal apparatus is lined with ciliated columnar epithelium. On coronal view (Fig. 9.2), there are

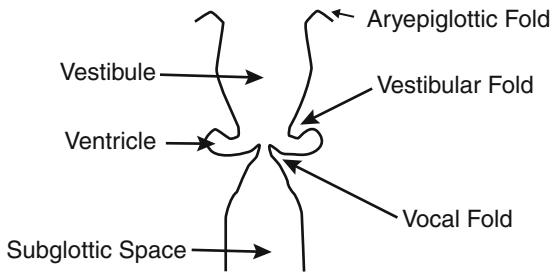

Fig. 9.2 Coronal view of the laryngeal apparatus

twofolds above the vocal folds; the paired aryepiglottic folds superiorly and the paired vestibular folds (structurally seen as false vocal folds) inferiorly. These supraglottic folds outline the vestibule. Below the vestibular folds are small cavities termed the ventricles that are bounded inferiorly by the vocal folds.

The Cartilaginous Framework of the Larynx

The structural skeleton framework of the larynx is composed of nine cartilages, along with their connecting membranes and ligaments. The three unpaired cartilages include the thyroid, cricoid, and the epiglottis, and the three paired cartilages are the arytenoids, corniculates, and cuneiforms.

The thyroid cartilage provides support for soft tissue structures. It is made of hyaline cartilage and consists of a pair of laminae that fuse inferiorly at an angle of 90 ° in men and 120 ° in women. Due to the sharper angle of fusion in men, the projection is much more prominent anteriorly and is commonly called the "Adam's Apple." The thyroid cartilage articulates with the cricoid cartilage on the medial surface and is further attached by the cricothyroid membrane. This thin membrane is near the surface of the skin, relatively avascular, and serves as the landmark for an emergent cricothyroidotomy. On the external lateral surfaces, there are ridges connecting the extrinsic laryngeal muscles: the sternothyroid, thyrohyoid, and inferior pharyngeal constrictor. The posterior margin of each thyroid lamina courses both upward and downward as superior and inferior cornua. The two superior horns suspend the larynx from the hyoid bone via lateral thyroid ligaments, and two inferior horns articulate with the cricoid cartilage.

The cricoid cartilage is situated below the thyroid cartilage and is the only complete cartilaginous ring. It is signet-ring-shaped and consists of an anterior arch and quadrilateral laminae posteriorly with superior articulating surfaces for the thyroid cartilage. It is also attached to the thyroid cartilage above by the median cricothyorid ligament and is attached to the first tracheal ring by the cricotracheal ligament.

Anterior cricothyroid pressure was advocated for patients who undergo rapid sequence intubation in order to prevent gastric content aspirations. However, the practice was originally described with small case series. In current practice, cricoid pressure should be practiced with caution as the maneuver has the potential to cause airway obstruction and make endotracheal intubations more difficult.

As described earlier, the cricoid cartilage is an important landmark for emergent cricothyroidotomy to rescue a difficult airway. However, subglottic stenosis can occur due to this procedure or in the cases of prolonged endotracheal intubation or tracheotomy that is performed too high (above first tracheal ring). In case of subglottic stenosis, surgical treatment with circumferential resection is not ideal. Instead, an anterior cricoid split is performed: a vertical anterior resection of the cricoid cartilage from the inferior aspect of the thyroid cartilage to the distal aspect of the stenotic segment. The membranous portion of the cervical trachea is preserved and used as a flap for reconstruction of the posterior cricoid plates.

The epiglottis is an elastic fibrocartilage with the superior free edge distal to the base of the tongue. It is lined with mucous membrane and is attached to the arytenoid cartilages by the aryepiglottic folds laterally on both sides. The anterior aspect of the epiglottis forms the inlet of the larynx.

Radiology of the Larynx

On axial view of computed tomography of the larynx, the epiglottis is seen at the level of the hyoid cartilage and separates the vallecula from the laryngeal vestibule (Figs. 9.2 and 9.3a–e). The valleculae are separated from one another by the glossoepiglottic ligament. Aryepiglottic folds appear at the anterolateral aspect of the larynx and are triangular in shape. They form a border between the laryngeal airway anteriorly and the piriform sinuses posteriorly (Fig. 9.3b). Supraglottic larynx consists of epiglottis, false/ventricular folds, aryepiglottic folds, and the arytenoids. Beneath this level is the glottis which consists of the true vocal folds, including the anterior commissure (Fig. 9.3c). Anterior commissure is the mucosa reflected from the anterior aspect of the true vocal folds, covering the posterior aspect of the thyroid cartilage in the glottis. Superiorly, the glottis is bound by the vocal cord epithelium which turns upward to form the lateral wall of the vestibules. The distinguishing feature between true and false vocal cords is the presence of fat in the false vocal cords (Fig. 9.3d). True vocal folds appear thin and elliptical in shape and are bounded by the thyroid cartilage anteriorly and thyroarytenoid muscles laterally.

Beneath the glottis is the subglottic region. It is the narrowest part of the airway and is situated between the vocal folds and the upper trachea. The subglottic space is circular in shape and is bounded posteriorly by the cricoid cartilage (Fig. 9.3e).

Muscles

The laryngeal muscles are divided into two groups: extrinsic and intrinsic muscles. The extrinsic group consists of the

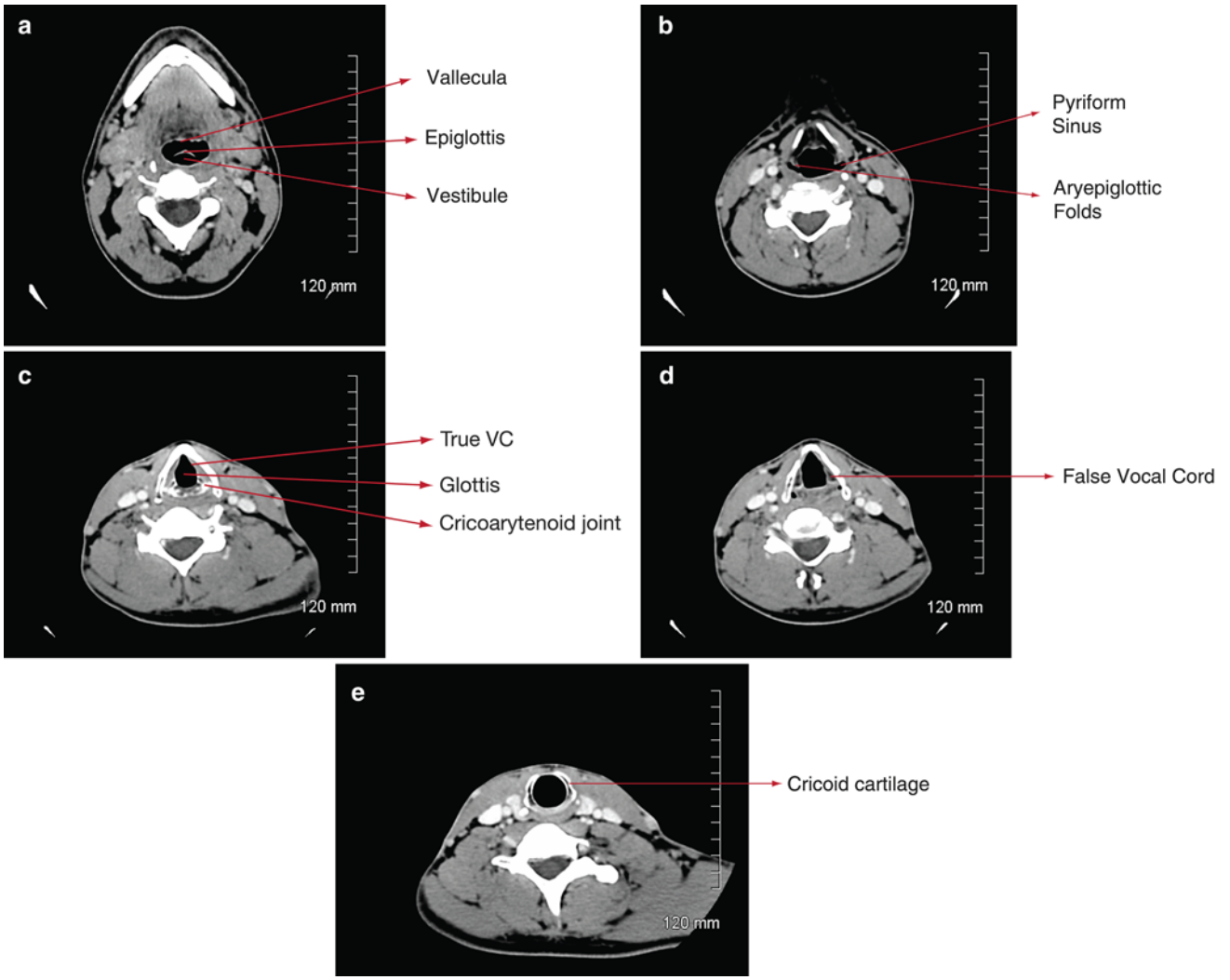

Fig. 9.3 Laryngeal CT images. (**a**) Main carina showing *left* and *right* main bronchi. (**b**) *Right upper* lobe segments showing typical trifurcation into apical, anterior, and posterior segments. (**c**) Distal bronchus intermedius showing *right middle* lobe, *right lower* lobe segments, and superior segment of the *right lower* lobes. (**d**) Distal *left* main bronchus showing the secondary carina leading to the *left upper* lobe and *left lower* lobes. (**e**) *Left lower* lobe segments showing the superior segment and the basilar segments

suprahyoid and infrahyoid muscles, and they are responsible for elevating and depressing, respectively, the laryngeal apparatus as a unit. The intrinsic muscles control the opening and closing of the glottis, as well as modulating the tension of the vocal cords.

The intrinsic musculature of the larynx controls the degree of opening of the glottis, as well as the tension of the vocal folds. The muscles always work in pairs. During inspiration, abductor muscles separate the arytenoids and open the glottis. During expiration, speech, and deglutition, the adductor muscles reverse the process to close the glottis. The tension of the vocal folds modulates airflow when they are adducted. The cricothyroid, vocalis, and thyroarytenoid muscles are responsible for tightening and relaxing the vocal folds for speech and phonation.

Lower Airway

Trachea

The adult trachea begins at the distal aspect of the cricoid cartilage, at the level of sixth cervical vertebrae, and ends at the main carina. The trachea is approximately 10–11 cm in length, with internal diameter of 16–20 mm. Sixteen to twenty U-shaped (or horseshoe) cartilages support the trachea (rings facing anteriorly), which bifurcates at the carina into the right and left main stem bronchus (Fig. 9.4). The trachea tapers slightly and aims posterior as it divides at the carina, at the level of fifth thoracic vertebra to the left and right main stem bronchi. The posterior part of the trachea consists of a smooth muscle (trachealis) that joins the ends of

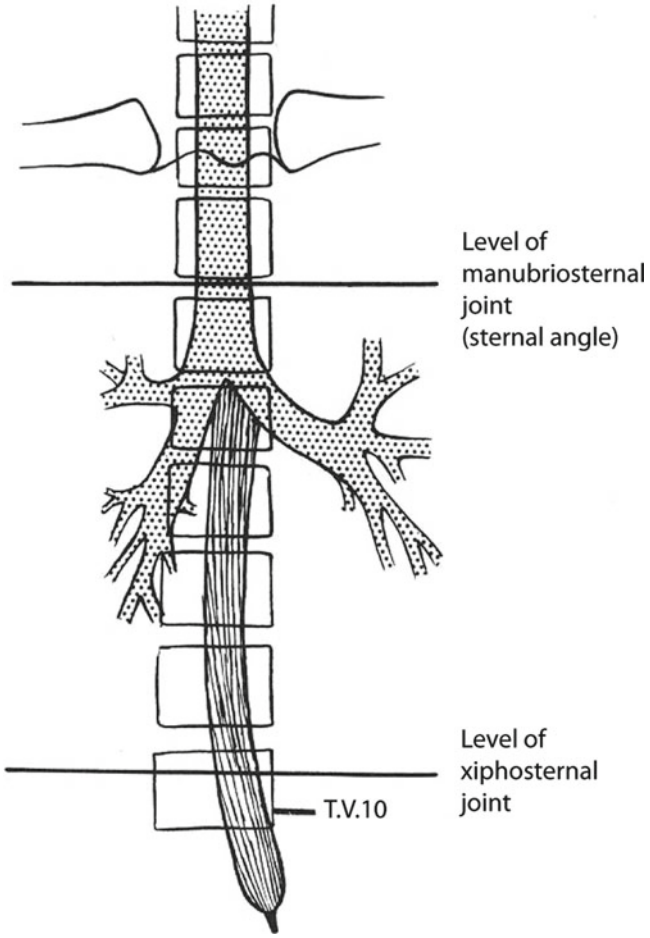

Fig. 9.4 The trachea and esophagus in relation to vertebral and sternal levels in a subject in the erect position (Reprinted with permission from O'Rahilly R, Müller F, Carpenter S, Swenson R. Basic Human Anatomy: A regional study of human structure. Copyright © O'Rahilly 2008)

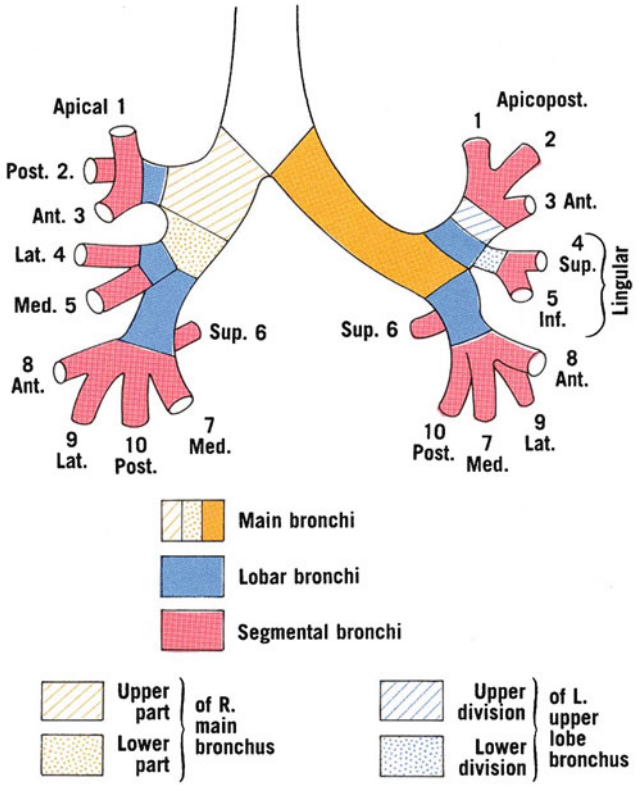

Fig. 9.5 Airway tree schematic (Reprinted with permission from O'Rahilly R, Müller F, Carpenter S, Swenson R. Basic Human Anatomy: A regional study of human structure. Copyright © O'Rahilly 2008)

the tracheal cartilage. The sagittal diameter is slightly longer than the coronal aspects, with the adult trachea measuring approximately 16 and 14 mm, respectively.

Tracheal Blood Supply

Branches of the inferior thyroid artery provide blood supply to the upper trachea and bronchial arteries supply the lower trachea (Fig. 9.5). The bronchial arteries additionally supply blood to the esophagus via anastamosis with the inferior thyroid artery. From the main carina onward, subsequent airway branches derive their blood supply from three bronchial arteries: two branches supplying the left lung and one branch supplying the right lung. The left bronchial artery originates from the descending aorta supplying the left lung. The right lung airways have various alternative supplies, including the aorta, first or third intercostal arteries, internal mammary artery, or the right subclavian artery.

The venous drainage of the airways contains a superficial and a deep system. The superficial system receives blood from the bronchial veins system of the hilum and the visceral pleura, which lead to the azgous vein with the right lung and accessory hemizygous vein of the left lung. The deep venous system drains the deeper tributaries and then directly to the pulmonary vein or the left atrium.

Endoscopic View of Trachea

Starting at the upper trachea, mucosal integrity should be examined, even when there are no gross endobronchial lesions. The presence of extrinsic tracheal deviation and compression due to paratracheal masses should be noted. Both the anterior cartilaginous and posterior membranous portion of the trachea is sometimes site for dynamic airway compromise caused by tracheomalacia or excessive dynamic airway collapse. Occasionally, nodular studding can be seen

that only localize to the cartilaginous rings while sparing the membranous portion of the trachea. This benign condition, called tracheopathia osteochondroplastica, is usually asymptomatic and found incidentally, accounting for approximately 2–7 per 1,000 cases of bronchoscopies.

Main Carina

The main carina is a keel-shaped structure oriented anteroposteriorly. It is usually sharp in adults, and its dimensions vary during inhalation and exhalation (Fig. 9.6a).

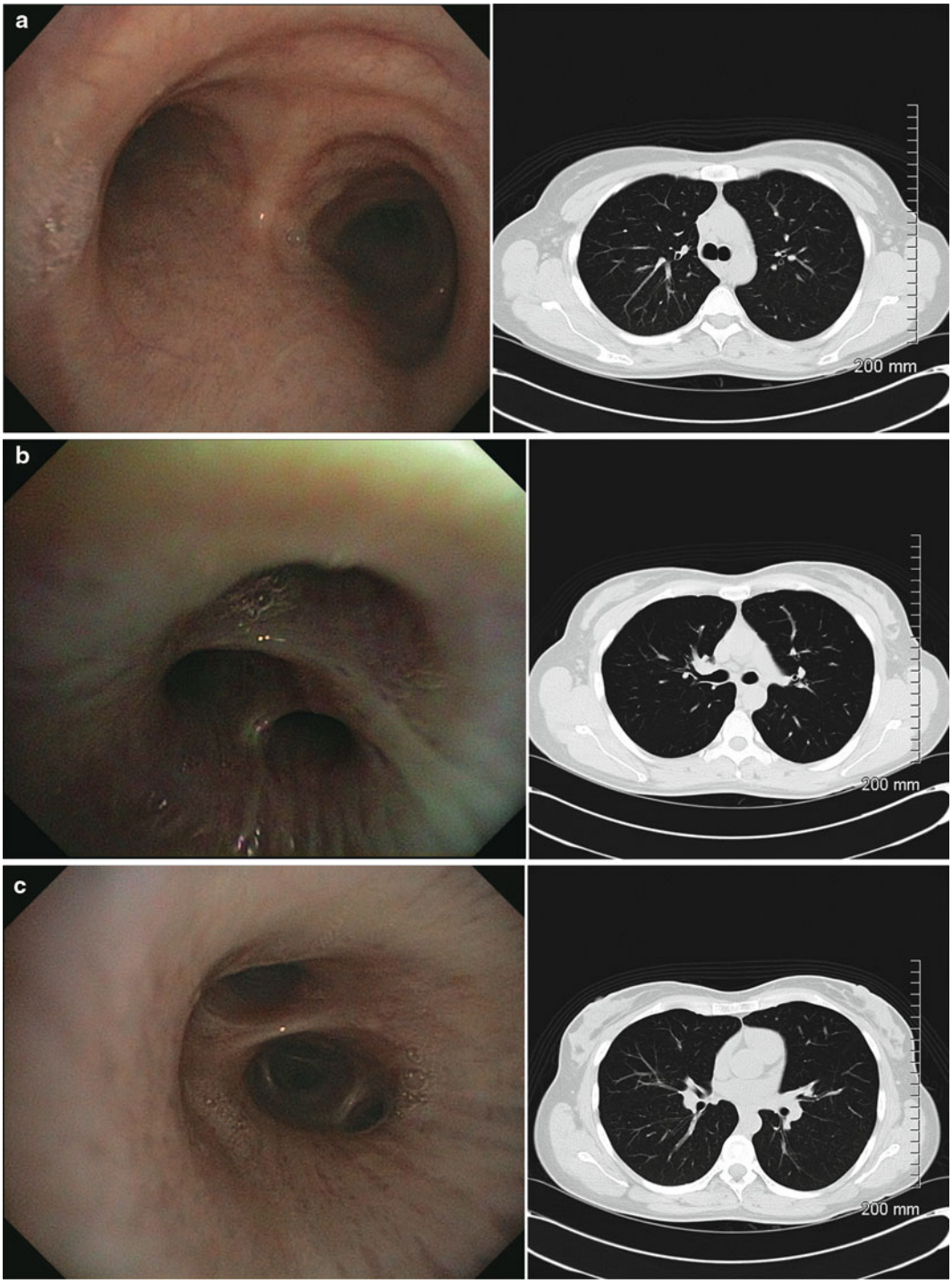

Fig. 9.6 (**a**) Carina with *right* and *left* main bronchi, (**b**) *right upper* lobe (B1: Apical, B2: Anterior, B3: Posterior), (**c**) *right middle* lobe and *right lower* lobe, (**d**) *left upper* lobe and *left lower* lobe division (B4: superior segment of LUL, B5: inferior segment of LUL, B6: superior segment of LLL, Apicoposterior segments not shown), (**e**) basilar segment of *left lower* lobe (B6: superior segment, B7,8: anteromedial segment, B9,10: lateral and posterior segment) (**d** and **e** Reprinted with permission from Kumaran R, Sung A, Ernst A. Airway anatomy for the bronchoscopist. In: Ernst AE, editor. Introduction to bronchoscopy. Cambridge, UK: Cambridge University Press; 2009)

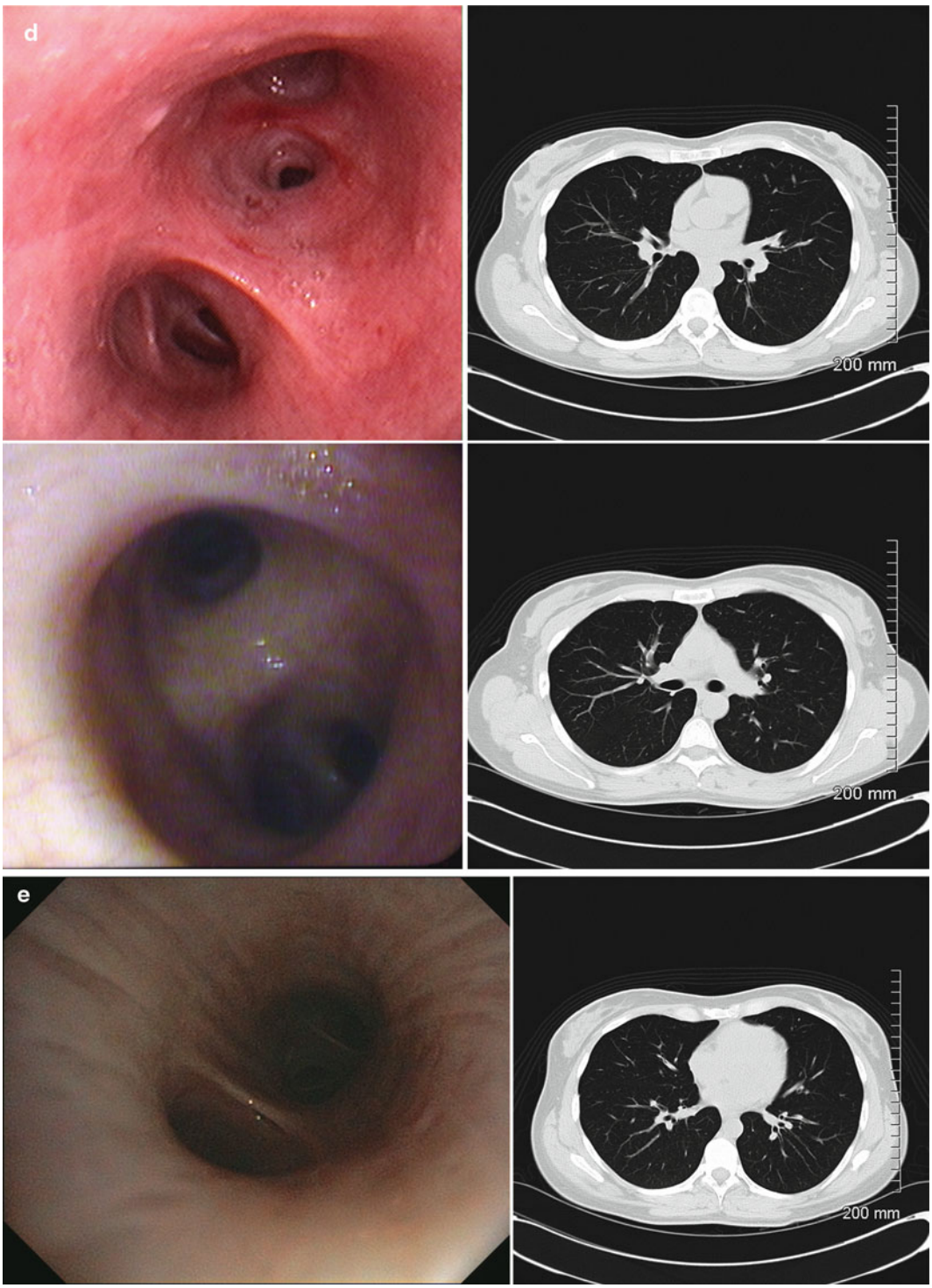

Fig. 9.6 (continued)

Classification of Bronchial and Segmental Airways

Bronchoscopists commonly refer to bronchial anatomy according to the Jackson-Huber classification of segmental airway anatomy (Table 9.1). This classification is named according to spatial orientation (i.e., anterior/posterior, superior/inferior, and medial/lateral) as listed in Table 9.1. Many thoracic surgeons prefer to use the Boyden surgical classification, which assigns numbers to the segmental airways. Bronchoscopists have commonly adopted the japanese nonmenclature, which assigns upper

Table 9.1 Segmental Airway nonmenclature/Jackson–Huber classification

Right bronchial tree		Left bronchial tree	
RUL		LUL	
B1	Apical	Upper division	
B2	Posterior	B1/2	Apicoposterior
B3	Anterior	B3	Anterior
RML		Lingular	
B4	Lateral	B4	Superior
B5	Medial	B5	Inferior
RLL	LLL		
B6	Superior	B6	Superior
B7	Medial basal	B7/8	Anteromedial
B8	Anterior basal	B9	Lateral basal
B9	Lateral basal	B10	Posterior basal
B10 posterior			

Note: *RUL* right upper lobe, *LUL* left upper lobe, *RML* right middle lobe, *RLL* right lower lobe, *LLL* left lower lobe

Source: Kumaran R, Sung A, Ernst A. Airway anatomy for the bronchoscopist. In: Ernst AE, editor. Introduction to bronchoscopy. Chapter 4, Table 4.1 Cambridge, UK: Cambridge University Press; 2009

lobe anterior and posterior segments as listed in Table 9.1 and as shown in Fig. 9.5.

Right Bronchial Tree

The right main bronchus is defined as the airway starting from the bifurcation of the trachea to the origin of the right middle lobe bronchus and the superior segment of the right lower lobe. It has a more vertical course as compared to the left main bronchus, forming approximately 25° to the plane of the trachea. The total length of the right main bronchus is approximately 5 cm, which includes the upper (giving off the right upper lobe) and lower part (giving off the right middle and lower lobes).

The first branch, the right upper lobe (RUL) bronchus, arises just below the carina and courses laterally for a distance of 1–2 cm before branching into apical, anterior, and posterior segments. The main bronchus then continues as the bronchus (or truncus) intermedius for approximately 2.5 cm before dividing into the right middle and lower lobes. Sometimes, a tracheal bronchus or an accessory bronchus is noted on CT scans arising immediately above the main carina and at the right lateral aspect. The accessory bronchus can be a source of recurrent or nonresolving infiltrate on chest radiograph, particularly in a young adult.

The right upper lobe bronchus is approximately 1 cm in length and divides into the apical, anterior, and posterior segments. The apical segment, or RB1, courses superiorly and divides into the anterior and apical subsegments. The posterior segment, or RB2, courses superoposteriorly and divides into the anterior and lateral subsegments. The anterior segment of the right upper lobe, or RB3, divides into anterior and lateral subsegments.

Beyond the RUL bronchus and the secondary carina, the right main bronchus becomes the bronchus intermedius, extends approximately 2–2.5 cm in length, and divides into right middle lobe and lower lobe bronchi. On chest CT, the branching point of the RUL bronchus can be identified as a faint curvilinear density marginating the lateral wall of the right main bronchus. The horizontal course of the RUL bronchus with origins of anterior and posterior segments gives the inverted whale tail appearance (Fig. 9.6b). On CT imaging, at the level of distal trachea, the apical segment appears as a circular lucency in proximity to pulmonary vessels. Both anterior and posterior segments can be easily seen. On chest CT, the bronchus intermedius is characteristically seen on several adjacent sections. It has an oblique shape and courses directly posterior to the right main pulmonary artery and the right interlobar pulmonary artery further inferiorly (at a lower level than the right main pulmonary artery).

The right middle lobe bronchus opening may have a "fish-mouth" appearance due to extrinsic compression by interlobar lymph nodes. Right middle lobe syndrome is clinically seen as recurrent infectious episodes due to postobstructive process from external compression of right middle lobe orifice. The right middle lobe bronchus divides and courses anterolateral-inferiorly and divides into the lateral and medial subsegments (RB 4 and 5, respectively) (Fig. 9.6c). The lateral segmental bronchus is visualized over a greater distance. The medial segment has a more oblique course and is less visualized.

The right lower lobe bronchus is further distal to the right middle lobe bronchus. The superior segment, or RB6, defines the posterior aspect of the termination of the bronchus intermedius. It arises at approximately the same level as the right middle lobe and is seen on the same plane on CT scan as the bifurcating segment. The superior segment courses horizontally and toward the posterior aspect and divides into the medial, superior, and lateral subsegments (Fig. 9.6d).

The distal to proximal configuration of the right lower lobes include the posterior, lateral, anterior, and the medial basal segments. The posterior segment courses inferiorly. The medial basal segment aims inferomedially, the lateral segment anterolaterally, and the anterior segment takes an anterolateral and inferior course.

Left Bronchial Tree

The left main bronchus is approximately 4–5 cm in length and tends to progress in postero-inferior-lateral direction. The diameter of the left main bronchus is slightly narrower compared to the right main bronchus and takes on a more horizontal course, forming an angle approximately 45 ° relative to the plane of the trachea. The left main bronchus is anterior to mediastinal structures including the esophagus, thoracic duct, and the decending aorta. It lies posterior to the pulmonary artery initially then courses posterior. At the level of the sixth thoracic vertebrae, it terminates as the secondary carina and divides into the upper and lower lobe.

The left main bronchus divides into left upper and lower lobe bronchi and is visualized during flexible bronchoscopy and on chest CT, as shown in Fig. 9.6e. The left upper lobe bronchus originates from the distal left main bronchus and divides into two bronchi that form the superior (apical) lobe of the left lung: anterior and apicoposterior segments. The anterior segment of the left upper lobe forms the upper lobe division of the left upper lobe, whereas the AP segments comprise the superior-posterior aspects (Fig. 9.6e). The anterior segmental bronchus is directed anteriorly and accompanied by the anterior segmental artery. As the upper lobe bronchus extends superiorly, the lingula branch arises and extends slightly downward in an inferolateral direction. The lingular bronchus is about 2–3 cm in length and divides into superior and inferior segments.

Left Lower Lobe

The superior segment of the left lower lobe bronchus arises immediately on entering into the left lower lobe. This is visualized during flexible bronchoscopy and on the chest CT. Beyond this, the left lower lobe bronchus is approximately 1 cm in length and divides into anteromedial, lateral, and posterior basilar segments. This is visualized during flexible bronchoscopy and on the chest CT.

Distal Airways

The bronchi are lined with smooth muscles and incomplete cartilage, with the mucosa lined with pseudostratified ciliated columnar cells with mucus-secreting glands. As the bronchi branch more distally and become devoid of cartilage, they become the bronchioles. The terminal bronchioles are located within the secondary lobules, or the Miller's unit, being the basic functional units. The respiratory bronchioles are divisions of the terminal bronchioles and are lined with alveolar ducts and sacs that are outpouchings and responsible for gas exchange.

Conclusion

Airway anatomy is the fundamental knowledge that is required for effective description of the upper airway and the tracheobronchial tree. Accordingly, meaningful differential diagnosis and clinical decisions are possible. Close communications with other specialties who confront airway pathologies are vital in care of patients affected with complex chest diseases.

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Bronchoscopy Education

10

Henri G. Colt

Experience is the name everyone gives to their mistakes.

– Oscar Wilde
(From Ladywindemere's Fan, Act III, 1892)

Background

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." While this well-known psychologist, social critic, and political activist was commenting on the practices of 1930s traditional versus progressive education in America's schools, his words still ring incredibly true today when applied to medical education and, more specifically, to procedure-related learning.

Surveys pertaining to flexible bronchoscopy conducted in countries as diverse as Singapore, Great Britain, India, Poland, Egypt, and the United States have consistently identified variations in practice and training. The diversity of the educational process is the consequence of 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 to be bronchoscopy instructors. Furthermore, the lack of a uniform competency-based framework for bronchoscopy education brings into question the rigor and effectiveness of many postgraduate programs that target physicians who wish to acquire new skills and procedures that can be introduced into their practices.

Traditionally, graduate medical education has been based on the Halstedt educational model of see one, do one, teach one implemented during a medical apprenticeship. This model which, until recently, has been employed on an almost universal and all but uncontested basis, was designed to replace the unstructured servitude in place until 100 years ago. It is based on the constraints of training for a fixed period of time, assimilation of material presented through more formal teachings, actual experience with patients, escalating responsibilities, and a period of supervised practice after training.

Bronchoscopy has been part of subspecialty training (for pulmonologists, intensivists, some surgeons, and anesthesiologists). Uniform, structured content is lacking, however. In addition, objective assessment tools have not been sufficiently explored. Training experiences and responsibilities are highly variable, and, at least in the United States, training program directors declare their trainee's competency and professionalism based on completion of their years of subspecialty training and a declaration of overall number of procedures performed (a number arrived at arbitrarily and based on the opinions of specialists but without actually measuring either technical skills or cognitive bronchoscopy-related knowledge). Furthermore, in the United States, while medical board examinations may contain a very sparse number of fact-based test questions, no assessment methodologies are used to ascertain procedure-related technical, experiential, or affective knowledge. Like other interventional procedures in medicine, physicians and surgeons, therefore, continue to work long hours, increasing their technical skill and experience one patient at a time.

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To enhance this experience, observerships might be sought at institutions around the world, providing practitioners with opportunities to seek the advice and technical expertise of procedure-savvy colleagues who might familiarize them with new procedures. This type of cultural interchange still exists today, not only enriching the knowledge and experience of health-care providers worldwide but also potentially placing physicians and patients into uncomfortable situations whereby patients are asked, if not inexplicitly told, that they must bear the burden of procedure-related training. During one's subspecialty training, patients might also be the unknowing victims of a physician climbing the learning curve of procedure-related skill and knowledge acquisition.

For health-care 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 (for both patient and physician). In addition, such a learning environment creates a difficult situation for a competent instructor, who knows that he or she can perform the procedure more quickly, more efficiently, and with greater patient comfort than the learner and yet intentionally refrains from interfering so that the physician-in-training might learn. The ethical dilemmas that ensue from such practices cannot be denied.

Of course, additional cognitive knowledge and familiarization with procedural techniques can also be gained from attendance at didactic lectures and workshops, as well as from hands-on training, which might take place during participation in postgraduate courses. At most postgraduate programs, course faculty present didactic lectures and direct group workshops, often consisting of 5–15 trainees per workstation, where they assist and instruct students in the actual procedure on inanimate and animal models. Until very recently, instruction would occur without a formal curricular structure that specifically emphasizes the informative, technical, affective, and experiential elements of knowledge, but in compliance with many continued medical education guidelines, specific objectives for didactic and hands-on session are identified, and course participants are asked to complete a critical review form in which they can point out the particular strengths and weaknesses of the program.

Organizing these programs is hard work, costly, and time-consuming, so it is not surprising that little attention has been paid to researching a program's efficacy, assessing the quality of teaching or the quantity and quality of knowledge and skills transfer and retention. In fact, it is usually assumed that knowledge and skill are acquired by course participants simply because they attended the program and only recently has there been an attempt to explore the use of competency-based metrics in interventional pulmonology-related postgraduate programs.

Changes in the perception of the educational process have been recently catalyzed by modifications of medical educational systems. In the United States, for example, The Accreditation Council of Graduate Medical Education has advocated a competency-based training model, replacing a model based on process and number of cases performed. Advances in, and an increasing acceptance of simulation technology have resulted in the expanded use of both lo- and hi-fidelity simulation, increasingly warranting that neither live animals nor live patients bear the burden of procedure-related training. In bronchoscopy, in fact, several computer-based simulation and inanimate models have been described and validated in specific settings. More widespread use of these and other models, in addition to affordable computer-based simulation, in this author's opinion, will result in greater concerted efforts to uniformize the global bronchoscopy educational process.

In the following paragraphs, I shall review some educational philosophies and methodologies. I shall then review some of the bronchoscopy education-related literature focusing on the use of simulation and competency-based metrics. Finally, in the last section of this chapter, I shall briefly illustrate the content of the recently released Bronchoscopy Education Project, reflect on how social media and web-based materials can be used by learners to expand their scope of practice, and describe several educational strategies and techniques that might be considered to enhance bronchoscopy education.

Philosophies and Methodologies

Procedure-related education, in my opinion, is more about learning than about teaching. While many parallels exist, learning a medical procedure is not the same as learning to play tennis, unless one is becoming a professional athlete. And just as we are not expected to immediately become champion tennis players invited onto the court at Wimbledon, we cannot be expected to become competent bronchoscopists simply by taking the scope in hand and moving to the patient's bedside. Using again the tennis analogy, learning requires acquisition of technical skill, facts (cognition), experience, and an understanding about how we actually feel about what we are doing (affect). The effectiveness of the learning process depends on elements of interaction between the learner and the learning environment; the frequency, variety, quality, and intensity of the learning encounter; the presence, quality, interest, skill, and demeanor of the teacher; the natural talents, genetics, and personality characteristics of the learner; the various means that are used to present learning materials (visual, auditory, multimedia, static, combined); and motivation (peer pressure, personal and third-party expectations, presence or absence of rewards, retribution, or consequences).

But similar to practicing a sport, learning can and should be fun. In this sense, the art of doctoring is learned, in part,

because doctors enjoy being doctors, caring for patients, and, when it comes to procedures, doing those procedures well. Thus, learning has intrinsic value. Learning to perform a medical procedure (meaning any type of minimally invasive or open surgical procedure whether performed by medical doctors or surgeons) is different, however, from a sport performed as a hobby, because a certain level of competence is expected, not only of ourselves but also by our colleagues, our patients, and society as a whole. In medicine, the road to mastery is not, as George Leonard says, "goalless." Rather, one must pursue a certain level of skill and knowledge that helps assure a level of competency that ensures patient safety, and our ability to efficiently and effectively reach a diagnosis or generally acceptable and expected therapeutic outcome.

- *Knowledge* generally applies to the body of information required by a physician in order to make a medical decision. In this regard, medical cognition refers to studies of cognitive processes such as perception, comprehension, decision-making, and problem-solving. Medical reasoning, on the other hand, applies to skills that enable a clinical decision. Regardless of whether a physician's training has been practice or science-based, the manner in which physicians reason is a direct consequence of the manner in which they have been educated.
- *Evaluation and assessment* apply to how we discover what and how much the learners are learning and how well they are progressing in their acquisition of knowledge and skills. *Low-stakes* testing usually does not have pass-fail thresholds, or carry significant consequences. In bronchoscopy training, for example, a validated *low-stakes* bronchoscopy skills and tasks assessment tool could be used to help trainees and faculty identify areas in which technical skill can be improved, while scores on a *low-stakes* written assessment could help trainees evaluate their progress in acquiring procedure-related knowledge and provide opportunities for instructors to provide constructive feedback. Such a program would be consistent with an educational process that emphasizes a quest toward professionalism and competency. A *high-stakes* assessment, on the other hand, usually carries significant consequences, such as licensure. High-stakes examinations are used to declare that a person has, for example, met the necessary qualifications to practice medicine. These are usually graded, have a pass or fail component, and are often mandatory in addition to other prerequisites such as number of years of training, or, in an apprenticeship model of instruction, number and quality of procedures performed. Assessments can also be used to ascertain curricular effectiveness, usually with the intent to modify and improve curricular structure and content based on the findings. For all such evaluation studies, significant problems and inaccuracies can arise depending on which outcome measures are used. These measures must be sensitive to the curriculum's stated goals and objectives, or to systemic factors such as outcomes that document a learner's progress through a system (within an institution or region for example).
- *Competency* is the ability gained from knowledge and skills, which form a basis for performance. To be competent means being able to activate and utilize that knowledge, when faced with a problem.
- *Competency-based education* warrants that each competency be teachable, learnable, and measurable. For example, it may or may not be expected that participants in a hands-on and didactic 1-day bronchoscopy program actually improve their knowledge and technical and decision-making skills significantly. On the other hand, it may be expected that participants in a pulmonary and critical care medicine fellowship program acquire competency in performing diagnostic flexible bronchoscopy independently. Agreement is lacking, however, in regard to core competencies versus the acquisition of optional skills. For example, what might be considered optional because of lack of resources or training opportunities in some countries (e.g., a procedure such as endobronchial ultrasound-guided needle aspiration) could be mandatory in others.
- *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 (accreditation council for graduate medical education). In this setting, *competencies* are defined as the specific knowledge, skills, behaviors, attitudes, and appropriate educational experiences required of trainees to complete graduate medical education programs.
- *Learning curve* was originally used to describe the rate of increase in the productivity of airplane manufacturing workers, who, while performing constantly the same procedure, typically become more efficient. In medicine, a learning curve, which might also be 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, circumstances, experience, and on whether the procedure being learned is new or established.[1] We increasingly tend to differentiate

[1] German psychologist Hermann Ebbinghaus (1850–1909) is credited with originally describing the learning curve in his work on memory (see RH Wozniak. Introduction to Memory. Classics in psychology 1855–1914: Historical essays. Bristol UK, Thoemmes Press, 1999). Learning curves can be mathematically calculated and may have different shapes representing incremental change, including a series of plateaus, rises and dips, and the traditional ogive "S"-shaped curve.

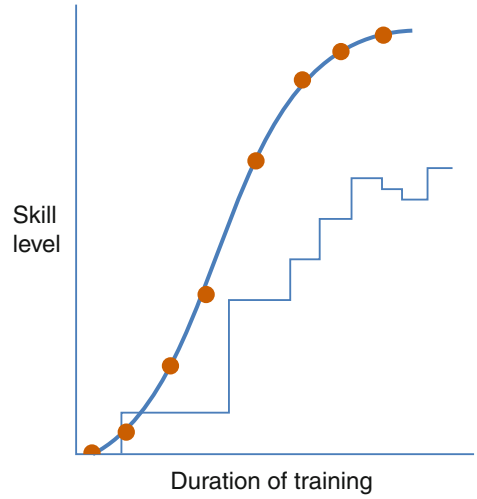

Fig. 10.1 Examples of ogive "S"-shaped learning curve and plateau with incremental gain and occasional dip (Courtesy of Dr. Henri G. Colt, MD)

learners into novices, beginners, intermediate learners, experienced, and experts, but categories such as beginner, intermediate, and competent can also be used. Learning curves are not always curves. Usually, progress is in spurts, or steps, with learners remaining or choosing to remain on a plateau that itself may have its occasional dips and peaks (Fig. 10.1). Diligent practice, time, and a focused quest for improvement will eventually result in a move to a higher plateau, only to be rapidly followed by a swift, and hopefully temporary, decline to another plateau, which, in many cases, can still be higher than the preceding ones. It is a fact that an expert in one technique may be a novice in another. Of course, it is possible that the expert will climb the learning curve more quickly than one who has no prior experience, but this can depend on one's area of expertise. For example, a young man with years of experience playing video games, may quickly become very good at two-dimensional video bronchoscopy, compared with an experienced surgeon who has worked constantly in a multidimensional open surgical world. This raises the issue that learning also depends on what has already been learned,[2] a paradox clearly identified by Plato in the dialogue *Meno*, when Socrates says

> I know, Meno, what you mean…you argue that a man cannot inquire either about that which he knows, or about that which he does not know; for if he knows, he has no need to inquire; and if not, he cannot; for he does not know the very subject about which he is to inquire.

[2] This is illustrated by 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).

Bronchoscopy-Related Education Literature

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 of 10 papers pertaining to the use of simulation for bronchoscopy education, we noted that simulation was demonstrated to help learners improve procedural efficiency and economy of movement, thoroughness, and accuracy of airway examination and decrease airway wall trauma. In addition to increasing learner satisfaction and interest, simulated environments create opportunities where tasks can be practiced repeatedly, risks to patients are eliminated, and training scenarios can be tailored to individual learners' needs. Both lo- and hi-fidelity simulation have been shown to enhance physician competency in procedural skills while saving time and improving the learning curve. While not yet shown conclusively in bronchoscopy, procedural skills acquired through practice on simulators are transferable to the clinical setting. In addition, simulator training with objective assessment and feedback identifies errors and provides opportunities for repeated and focused practice without exposing patients to unnecessarily prolonged procedures and discomfort.

Hi-fidelity simulation platforms using three-dimensional virtual anatomy and force-feedback technology can be used, for example, to teach conventional transbronchial needle aspiration (TBNA), although less expensive, lo-fidelity models comprised of molded silicone or excised animal airways are also effective. We demonstrated the efficacy of a lo-fidelity hybrid airway model made of a porcine trachea and a plastic upper airway for learning transcarinal and transbronchial needle aspiration. 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 nonhospital facilities. Models can be used to teach scope manipulation and airway anatomy, foreign-body removal, bronchoscopic intubation, endobronchial ultrasound-guided TBNA, and various other interventional techniques (Fig. 10.2). In fact, based on learner and instructor perceptions, a lo-fidelity model was shown to be superior to costly hi-fidelity computer simulation for learning three different conventional TBNA techniques.

Demonstrating improvements in technical skill complete only part of the picture. The increasing emphasis on competency-oriented education also warrants that bronchoscopy courses use competency-based measures to assess the efficacy of course curricula and training

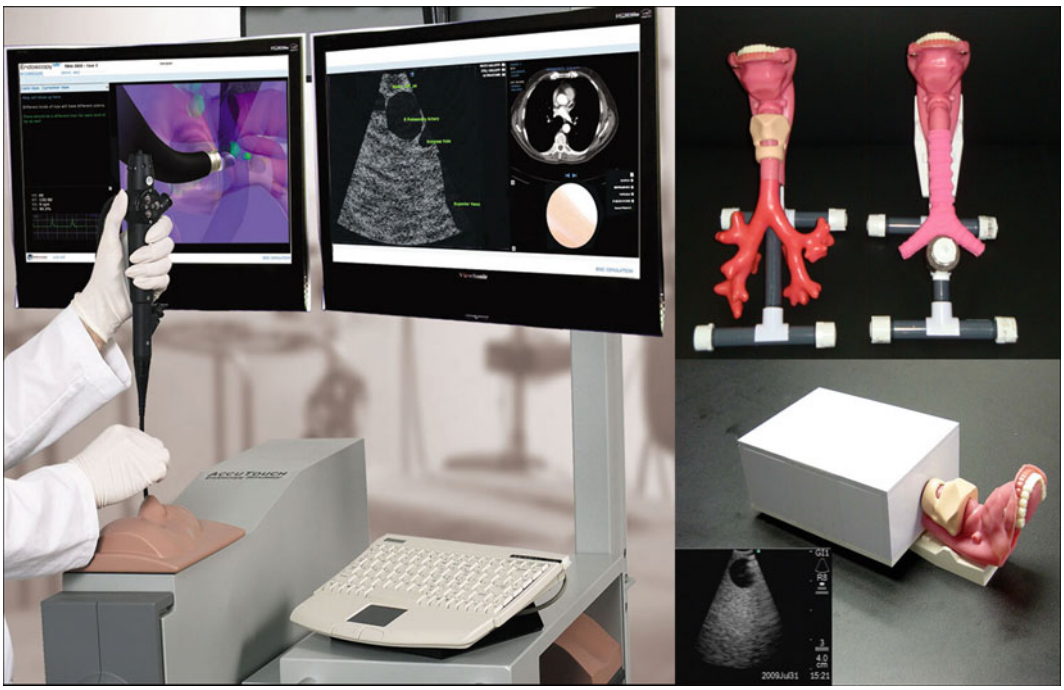

Fig. 10.2 Examples of hi-fidelity and lo-fidelity models for teaching bronchoscopic inspection, conventional transbronchial needle aspiration, and endobronchial ultrasound (Courtesy of Dr. Henri G. Colt, M.D.)

modalities. 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. Using quasiexperimental study design and a series of pretest/posttest assessments with 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. Studies are ongoing to determine how various elements of knowledge can be assessed using components of the Bronchoscopy Education Project described later in this chapter[3] (Figs. 10.3, 10.4, and 10.5).

Description of a Transnational Education Initiative

The Bronchoscopy Education Project[4] entails the design, development, and dissemination of a series of structured, uniform curricula that include required reading assignments, simulation scenarios, standardized didactic lecture material, validated assessment tools, and checklists (Fig. 10.3). The purpose of this project, officially endorsed by several international bronchology and interventional pulmonology societies, is to provide bronchoscopy educators and training program directors with competency-oriented tools and materials with which to help train bronchoscopists and assess progress along the learning curve from novice to competent practitioner. Material can be incorporated in whole or in part, as needed by each program. Learning is based on the review of written materials, focused practice during hands-on programs and during the course of subspecialty training, and through easy access to educational materials as available at specifically designed websites, YouTube, and Facebook.

In addition to many written materials and structured didactic lectures provided through regional on-site programs, a free, web-based six-part curriculum is being developed with the assistance of numerous experts from around the globe.

[3] Cognitive knowledge could be assessed using standardized testing with written multiple-choice questions and oral interviews. Test questions should ideally be validated using specific criteria that include testing for difficulty and internal reliability. Technical skill assessments can be used to document progress along the learning curve, using measures that are validated and reproducible and have a strong correlation to the procedure being taught. Various Bronchoscopy Assessment Tools© can be used to document improvement in dexterity, accuracy, speed, position and posture, economy of movement, atraumatic instrument manipulation, anatomic recognition, and navigation. Checklists can be used to ascertain competency in various components of a procedure such as ability to obtain informed consent or safe use of fluoroscopy. Experiential and affective knowledge can be explored using graded patient-centered learning exercises and structured simulated clinical scenarios.

[4] For more information, search Bronchoscopy International on YouTube and Facebook, or go to www.Bronchoscopy.org.

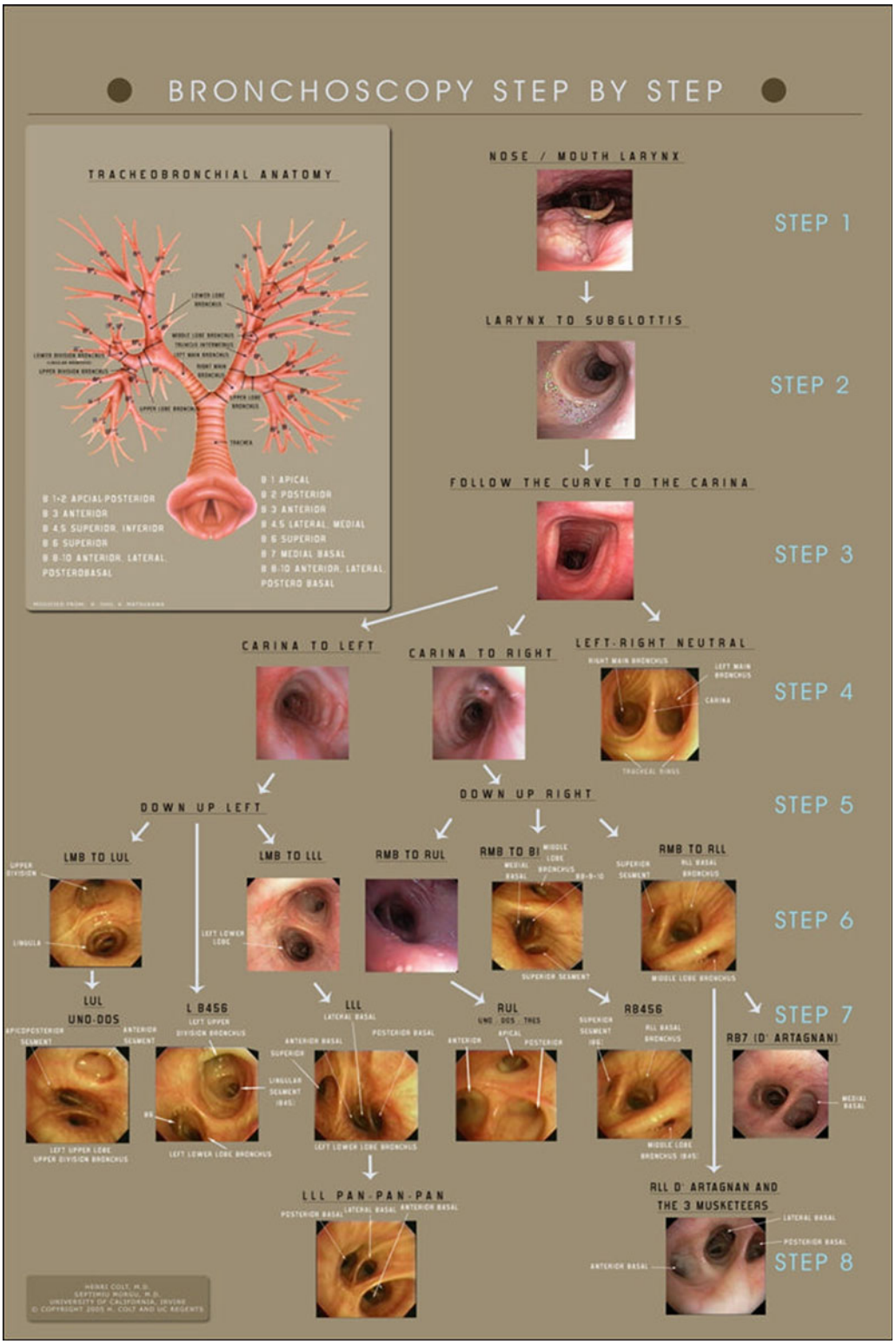

Fig. 10.3 Example of Bronchoscopy step-by-step instruction. Colt HG. *Bronchoscopy Lessons.* Instructional video pertaining to various aspects of bronchoscopy You Tube (posted 2010): http://www.youtube.com/watch?v=phRv73Ik7fI&feature=related (Courtesy of Dr. Henri G. Colt, M.D.)

FLUOROSCOPY 10-Point CHECKLIST*

Student _____ Training Year _____

Faculty _____ Date _____

☐ Interactive session ☐ Patient environment

Educational Item* Items 1–10 are scored 10 points each (no partial points given)	**Satisfactory Yes/No**
1. Able to list indications for using fluoroscopy	Yes / No
2. Able to describe the relevance of voltage and amperage ☐ For image quality ☐ For patient safety	Yes / No
3. Able to describe consequences of resolution, distortion, and lag ☐ For image quality ☐ For patient safety	Yes / No
4. Able to describe consequences of brightness and contrast ☐ For image quality ☐ For patient safety	Yes / No
5. Able to describe dangers of scattered radiation	Yes / No
6. Able to describe techniques to improve visibility of fluoroscopic image	Yes / No
7. Able to describe techniques used to reduce patient radiation exposure	Yes / No
8. Able to describe techniques used to reduce operator radiation exposure	Yes / No
9. Able to describe special precautions in case of suspected or known pregnancy ☐ Patients ☐ Health care providers	Yes / No
10. Able to describe basic operation procedures	Yes / No

* Each of the 10 items contains all of the elements required by ACGME(patient care, medical knowledge, practice-based learning and improvement, interpersonal communication skills, professionalism, and systems-based practice).

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

Fig. 10.4 Example of checklist used as part of The Bronchoscopy Education Project. See Colt HG. *Bronchoscopy Education Project Rationale*. Instructional video You Tube, posted July 2010: http://www.youtube.com/watch?v=ogRixvyTYEA (Courtesy of Dr. Henri G. Colt, M.D.)

Procedures are deconstructed into three elements: strategy and planning, technical skills, and outcomes assessment (results, quality control, ability to respond to complications, and long-term management). In order to identify elements crucial to medical reasoning when entertaining a bronchoscopy consultation, these elements are further divided into four categories using a four-box *Practical approach to procedural decision making*: patient evaluation, procedural strategies, techniques, and outcomes. A series of practical approach exercises is one of the six elements of the web-based curriculum. Other elements are:

The web-based *Essential Bronchoscopist*© and *EBUS Bronchoscopist*© comprised of specific reading materials, learning objectives, and post tests. Each module contains numerous question-answer sets with information pertaining to the major topics relating to bronchoscopic procedures (anatomy and airway abnormalities, patient preparation, indications, contraindications and complications, techniques and solutions to technical problems, disease states, imaging, procedural techniques, anesthesia and medications, equipment and its maintenance, as well as history and education). The aim of these modules is not to replace but to complement the subspecialty bronchoscopy training environment and motivate learners to ask questions of their preceptors and colleagues.

A *Bronchoscopy Step-by-Step*© and *EBUS Step-by-Step*© series of graded exercises help learners acquire the technical skills necessary for basic diagnostic bronchoscopy. Instructional videos are readily viewable on desktop computers as well as handheld devices, IPADs, or cell phones. Specific training maneuvers help the learner practice incrementally difficult steps of bronchoscopy and EBUS-TBNA. 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.

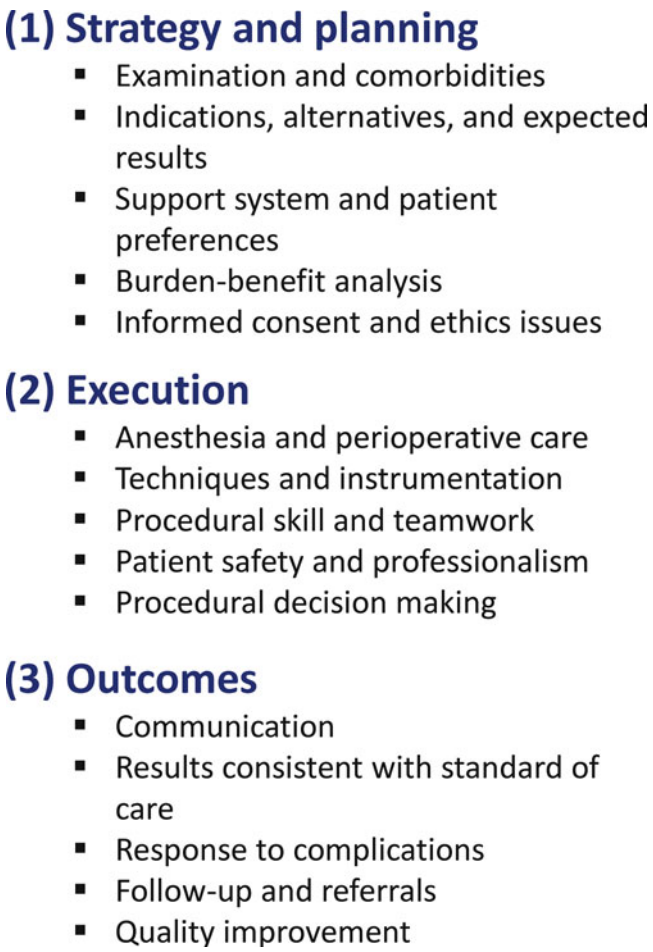

Fig. 10.5 Deconstruction of a bronchoscopic procedure to enhance patient-centered learning and educational interventions within the learner's zone of proximal development (Courtesy of Dr. Henri G. Colt, M.D.)

A series of *Bronchoscopy Assessment Tools*© provide objective measures with demonstrated validity and interobserver reliability. Fixed numeric and grade scores can be attributed to the learner based on technical skills that include dexterity, accuracy, anatomic recognition and navigation, posture and position, economy of movement, and atraumatic instrument manipulation, pattern recognition, and image analysis.

Two additional elements are *The Art of Bronchoscopy*© and *BronchAtlas*© series of PowerPoint presentations pertaining to airway pathology, normal airway examination, and techniques of basic diagnostic and therapeutic bronchoscopic procedures. The goal is to provide free access to edited images and scientific content so that bronchoscopists might freely use materials for their own education and also to facilitate their efforts while preparing lectures within their own institutions and national societies, thereby increasing awareness of both the art and science of bronchoscopy in their communities.

Learner-Teacher Interactions Define Bronchoscopy Education

The experiential learning necessary to become a competent bronchoscopist includes passive experiences (something that happens to or is delivered onto the learner) and interactive processes (something in which the learner is actively engaged mentally, physically, and emotionally). Dewey called this learner-focused activity "learning by doing," also suggesting that thinking is stimulated by problems the learner is interested in solving. For medical practitioners dedicated to the health and well-being of their patients, learning in this way obviously creates intrinsic value and serves to enhance the learning process.[5]

As our understanding of what we are doing increases and as we move toward becoming one with the activity at hand, we can become increasingly aware of the intrinsic value of that activity in our lives. Wolfgang Kohler, a German Gestalt psychologist (1887–1967) noted that such insight, defined as a way for "seeing" the link between certain ideas, is crucial to the learning process because learning is more than the simple reinforcement of our operant behaviors.

For unspecified reasons, physicians are expected to be good mentors and effective instructors without ever having learned to teach. Such an approach to the learning process runs contrary to practice in other fields (such as public school education, hobbies, or sports) and represents a significant shortcoming of our academic institutions and profession. As knowledge becomes more universally available, the attitudes and behaviors of health-care providers will change accordingly not only toward patients but also toward the next generation of medical practitioners. Learners are already less dependent on rote memorization, referring frequently to web-based instruction, electronic information delivery systems, and social media available through their computers or handheld devices. Educators will need to become more

[5] The constructivist psychologist Lev Vygotsky (1896–1934) believed that learning and development depend on social interaction. Focusing primarily on how children learn, he described a zone of proximal development (ZPD) as "the distance between the actual development level as determined by independent problem solving and the level of potential development as determined through problem solving under adult guidance or in collaboration with more capable peers" (L.S. Vygotsky: *Mind in Society: Development of Higher Psychological Processes*, p. 86, John-Steiner, Cole, Scribner, and Souberman Editors, Harvard University Press ,1980). Tinsley and Lebak expanded on this theory, 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 working environment (Lebak, K. & Tinsley, R. Can inquiry and reflection be contagious? Science teachers, students, and action research. Journal of Science Teacher Education;2010: 21;953–970).

proficient at the delivery of educational materials and focus on global measures of competency and professionalism that reflect more than might simple grade scores on a multiple-choice examination. An emerging interest in new leadership development programs, specifically designed train-the-trainer seminars, and well-planned teaching scenarios that allow bronchoscopy educators to become familiar with and experiment with various educational approaches, therefore, will likely improve the educational process for physicians-in-training as well as for experienced bronchoscopists desiring to master a new procedure.

Dewey compared a *traditional* educational approach, whereby learners are meant to master educational content delivered from a teacher-knows-best perspective, often using conventional methods of instruction, to a *progressive* approach, whereby teachers try to focus attentions on the explicit needs and interests of their students. Fenstermacher and Soltis describe a third, *humanistic* approach, whereby teachers strive to impart knowledge within an environment in which learning has personal meaning for the learner, helping the learner gain his or her own knowledge and skill.

Regardless of the approach, several teaching techniques described in general education can be employed in medical procedure-based instruction. In the *facilitator* technique, for example, the instructor assumes that the learner has already acquired certain knowledge. In bronchoscopy, this might be achieved by insisting and perhaps verifying that learners view instructional videos and complete mandatory reading assignments prior to an on-site educational intervention. The instructor guides, nurtures, and encourages student-driven learning through constant and for the most part, positive feedback. During hands-on instruction, an instructor could avoid handling the bronchoscope (a true hands-off technique for the teacher), letting instead the learners maintain control as they are individually coached through the resolution of skill-based problems (a truly hands-on technique for the learner).

In other instances, an *executive* technique might be used; its efficacy often measured by how much knowledge is actually gained by the learner. This strategy includes the planning, execution, and assessment of a variety of educational interventions. Opportunities are created whereby the learner has a chance to actually learn what is being taught. For example, a curriculum might be intentionally constructed to assure repetition and reinforcement, checklists might be used to assure that each step of a particular technique is mastered before moving on to the subsequent step, and active engagement time, defined as the amount of time actually spent learning by the learner, could be maximized. Returning to the example of a hands-on workshop, learners could be exposed as a group to baseline instructions, demonstrations, and learning objectives using web-based materials prior to coming to an individual workstation. This would allow station instructors to devote all of their time to teaching specific aspects of the task at hand, avoiding small talk, unhelpful anecdotes, or storytelling. Checklists could be completed to document skill acquisition (Fig. 10.4). It is noteworthy that a workshop that allows 50 min for five learners, in the best of cases, provides only 10 min of actively engaged time per learner undergoing one-on-one individual instruction. One wonders how much is actually being learned by the majority of workstation participants during the other 40 min.

While Ferstermacher and Soltis's facilitator approach values how the learner feels as a person, the executive strategy emphasizes the acquisition of knowledge as an end in itself. A third, *liberationist* approach dares to challenge the learner to create, imagine, and wonder in an attempt to understand and gain knowledge of the task at hand. Rather than demonstrate, for example, how a specific technique is performed, the instructor might ask the learner to discover his or her own way of demonstrating the skill comfortably and without traumatizing the airway or jeopardizing the equipment. Rather than giving strict instructions of procedural technique based on "this is how we have always done it," the instructor might instead share general principles with the learner, such as "think of what you are going to do rather than just doing it," "think of and demonstrate various ways this could be done atraumatically rather than just doing it," and "perform the procedure with ease and greatest economy of movement."

Conclusion

It is a paradox that a profession that constitutes caring for other human beings is essentially learnt by forcing many patients to bear the burden of procedure-related training. As the use of alternative learning methodologies such as practicing on models, computer-based simulation, small group patient-centered discussions, and fingertip availability of media-based instruction are explored and their efficacy demonstrated, learning bronchoscopy through trial and error purely at the patient's bedside will become increasingly unjustifiable normatively. By this, I mean in the sense that learning *on the job* will no longer represent what ideally *should* or *ought* to be done.

The paradigm shift in bronchoscopy education is therefore unavoidable. Overall scope of practice will also be enhanced, as bronchoscopists become increasingly familiar with the language and tools of the education process: train the trainer programs will become necessary to assist potential educators in their efforts to effectively deliver program content and build competency-oriented programs within their own institutions and regions. Uniformization of educational content and process will facilitate social interactions,

knowledge transfer, and equality of care in a global community. Bronchoscopy educators will learn how to alternate between various instructional techniques dependent on the learning context and educational strategy employed. Hopefully, our medical societies, subspecialty organizations, and universities will look favorably[6] on those motivated individuals willing to commit time, energy, and a major component of their academic careers to the training of a new generation of bronchoscopists who will learn without putting their patients in peril.

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[6]By this, I imply financial support and recognition through faculty development programs and academic promotions and through a willingness to publish education-related research and commentaries.

Simulation for Endoscopy Training

11

Momen M. Wahidi

Introduction

Bronchoscopy is a common procedure, with an estimated 500,000 bronchoscopies performed annually in the United States. It is mainly performed by pulmonologists, but surgeons, anesthesiologists, and intensivists also perform this procedure for a variety of diagnostic and therapeutic purposes. Acquisition and maintenance of bronchoscopy skills for both novice and advanced learners is an issue of high priority to ensure optimal delivery of health care and reduce errors and complications. Simulation presents a new option in the armamentarium of skill teaching and is positioned to play an essential role in the education of current and future physicians. In this chapter, I will review the current state of bronchoscopy training and the evolving role and data on simulation in bronchoscopy.

Current Training of Bronchoscopy

There are currently no published guidelines for bronchoscopy training. In 2003, the American College of Chest Physicians recommended the number of yearly procedures needed to establish or maintain competency in advanced bronchoscopic procedures.

Flexible bronchoscopy training for pulmonologists in the USA takes place during a 2–3-year fellowship following internal medicine residency. The Accreditation Council for Graduate Medical Education (ACGME) requires the performance of 100 bronchoscopies per pulmonary trainee in order to graduate. The current method of learning bronchoscopy relies on the traditional apprenticeship model, the so-called "see one, do one, teach one" philosophy.

In this model, the learners acquire some basic understanding of the procedure by simple observation then hone their skills by practicing on patients under faculty supervision. No prior training or assessment of the learners is usually carried out or required prior to performing the procedures on patients.

The advantage of this teaching model is the opportunity for the learner to learn directly from a skilled operator with one-on-one mentoring; however, the disadvantages are abundant including the lack of consistency in teaching methodology across training centers, subjective evaluation of skill acquisition, and unnecessary and taxing practice on individual patients.

A few surveys of pulmonary fellows' bronchoscopy training over the last decade found that most procedural training is obtained "on the job" via individualized instruction from faculty; very few training programs offered structured curriculum or hands-on experience at the onset of training.

Competency in bronchoscopy among trainees is currently established based on procedures' number and a global subjective assessment of faculty observers. Pulmonary fellowship training programs require the performance of at least 100 bronchoscopies for pulmonary trainees to achieve competency.

A number-based competency metric does not test the cognitive component of procedural learning, nor does it account for variation in the number needed for an individual learner to acquire a skill.

Emerging Tools for Bronchoscopy Education

Realizing the limitation of the apprenticeship model, educators have sought other venues to provide practical education of bronchoscopy. These include extracted and preserved animal lungs, live animals, cadavers, inanimate airway models, and airway simulation software. While the first three options

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can be effective teaching tools, they are fraught with issues such as ethics of animal and human tissue use, durability of models, infectious risks, and the burden of regulatory oversight. The use of airway models or airway simulation software, lo- or hi-fidelity simulation respectfully, eliminates these issues and represents an effective alternative for the teaching of bronchoscopy.

Simulation in Bronchoscopy Education

Simulation offers an effective method of teaching procedural skills which avoids using animals and offers a scenario-based interaction that imitates real-life situations. Other disciplines, such as the aviation industry, where errors also can have serious consequences rely heavily on simulation learning and assessment of continued competence.

Simulation technology in bronchoscopy is available in two forms: lo-fidelity inanimate mechanical airway models and hi-fidelity computer-based electronic simulation.

Lo-fidelity Simulation

Lo-fidelity models consist of molded tracheobronchial trees that offer realistic tubular-shaped airway-like structures with accurate anatomy to the first subsegmental bronchial level. Figure 11.1 shows an example of such a model, the CLA Broncho Boy (CLA, Coburg, Germany). A lo-fidelity model can be an excellent tool for novice operators to memorize airway anatomy, build muscle memory, and enhance hand-eye coordination. Lo-fidelity simulation offers a cheap alternative to the costly hi-fidelity simulation and can be effective in teaching bronchoscopic skills. The main disadvantage is the lack of interactive capability which limits situational learning and the limited ability to teach various iterations of the airways including abnormal anatomy or pathologic findings.

Domenico et al. were able to build a real-scale anatomically accurate bronchoscopy model that cost less than $30 by utilizing iron wires, newspaper sheets, and glazier putty. Goldberg and colleagues built a hybrid model, connecting a plastic tongue and larynx to a porcine trachea and main-stem bronchi as a teaching tool for transbronchial needle aspiration (TBNA) for <$200; the model was viewed, by novice and experienced learners, as realistic and helpful in improving TBNA skills.

In the only study that compared lo- and hi-fidelity simulator as teaching tool in bronchoscopy, the author of this chapter and his colleagues performed a prospective randomized crossover design to train study participants in three methods of conventional TBNA using lo- and hi-fidelity models. Learners felt the models were equally enjoyable and enthusiasm generating but preferred lo-fidelity models in terms of realism and ease of learning. Instructors shared this sentiment with the students and regarded the lo-fidelity model as a more effective teaching instrument for TBNA. This preference for lo-fidelity simulation in this study is not generalizable to all aspects of bronchoscopy learning, but it highlights the effectiveness of lo-fidelity models in procedures that require some tactile feedback such as TBNA (needle insertion through tissue).

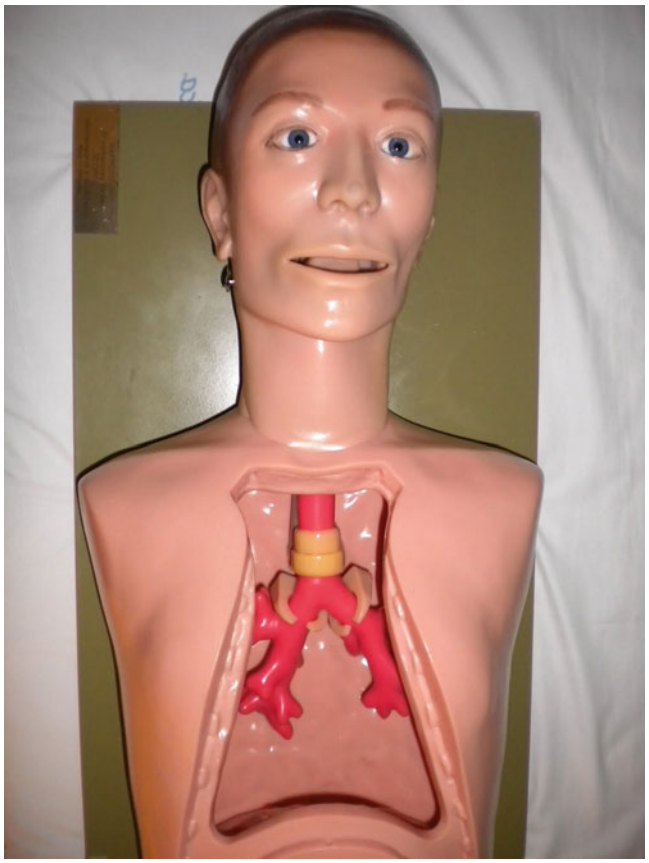

Fig. 11.1 A lo-fidelity mechanical airway model for bronchoscopy teaching

Hi-fidelity Simulation

Hi-fidelity simulators are computer-based and rely on the same technology as video games. The bronchoscopy simulator consists of a proxy bronchoscope, a robotic interface device, and a personal computer with a monitor (Fig. 11.2). The proxy bronchoscope is inserted into a plastic face and is maneuvered on the computer screen into a 3-D image recreation of the airways (Fig. 11.3). The robotic interface device tracks the motions of the bronchoscope and reproduces the force felt during an actual bronchoscopy. The "virtual" patient on the screen breathes and coughs, and the vital signs

Fig. 11.2 A hi-fidelity computer-based simulator for bronchoscopy teaching (Pictures taken using Simbionix' BRONCH Mentor simulator)

are monitored in real time. Various standardized scenarios are offered, and the learner can choose to examine normal airways, intubate difficult airways, perform brushing or biopsy on an endobronchial tumor, or sample an enlarged lymph node via TBNA (Fig. 11.4). The bronchoscopy simulator also offers anatomic labels on the airway branches and the structures adjacent to the airways to help the learner to become skilled at recognizing anatomy of normal structures; this feature can be turned on or off based on the learner's level of knowledge and educational needs.

The software tracks performance metrics such as time of procedure, amount of used lidocaine, incidence of wall collision, percentage of segments entered, and success in obtaining a sample from a targeted lymph node.

There are two commercially available hi-fidelity systems in the USA: the Endoscopy VR simulator (CAE Healthcare, Montreal, Quebec, Canada) and the GI-BRONCH Mentor (Simbionix Ltd, Israel).

Hi-fidelity simulation offers numerous advantages including repetitive practice, training in a safe stress-free environment, exposure to rare or difficult scenarios, and receiving immediate feedback on performance.

The data for hi-fidelity simulation in the learning of various medical and surgical procedures are abundant; there have been numerous publications showing the efficacy, cost-effectiveness, and increase in patients' comfort and safety when simulation-based training is undertaken by trainees.

The first reports of the efficacy of the bronchoscopy hi-fidelity simulator were published in 2001. Colt and colleagues reported the outcomes of five novice bronchoscopists who received 4 h of training on a bronchoscopy simulator and then spent 4 h practicing on their own without supervision; bronchoscopy skill sets obtained by the novices (dexterity, speed, and accuracy) reached those of a control group of skilled bronchoscopists (who had performed at least 200 bronchoscopies) after only 8 h of training. Ost et al. validated the bronchoscopy simulator as an assessment tool and demonstrated its ability to discriminate among bronchoscopists with varying levels of bronchoscopy skills; the study found that expert bronchoscopists (>500 bronchoscopies) performed better than intermediates (25–500) who in turn performed better than novices.

Most recently, the author of this chapter reported the first prospective multicenter study of performance-based metrics and educational interventions in the learning of bronchoscopy among starting pulmonary fellows. In this study, two successive cohorts of starting pulmonary training were enrolled in the study.

At prespecified milestones, validated tools were used to test their bronchoscopy skill and knowledge: the Bronchoscopy Skills and Tasks Assessment Tool (BSTAT), an objective validated evaluation of bronchoscopy skills with scores ranging from 0 to 24, and written multiple-choice question examinations.

The first cohort of fellows received training in bronchoscopy as per the standards set by each institution, while the second cohort received training in simulation bronchoscopy and was provided an online bronchoscopy curriculum. There was significant variation among study participants in bronchoscopy skills at their 50th bronchoscopy, the number previously set to achieve competency in bronchoscopy. An educational intervention of incorporating simulation bronchoscopy enhanced the acquisition of bronchoscopy skills, as shown by the statistically significant improvement in mean BSTAT scores for seven of the eight milestone bronchoscopies ($p < 0.05$). The online curriculum did not improve the performance on the written tests; however, compliance of the learners with the curriculum was low.

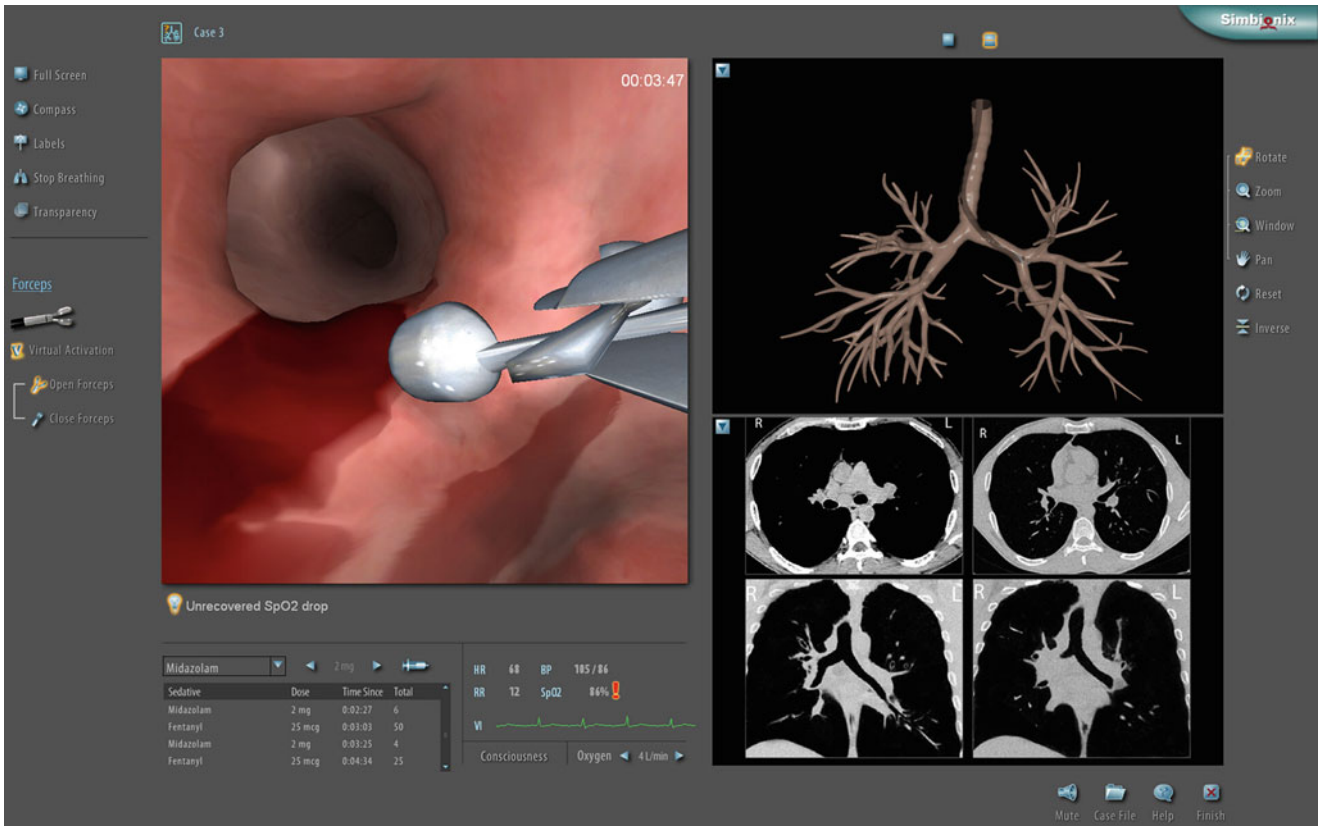

Fig. 11.3 The monitor screen of a hi-fidelity simulator showing a 3-D virtual image of the airways (Pictures taken using Simbionix' BRONCH Mentor simulator)

Fig. 11.4 A learner practices her bronchoscopy skills on a hi-fidelity computer-based simulator (Pictures taken using Simbionix' BRONCH Mentor simulator)

Simulation for Advanced Bronchoscopic Procedures

There has been a rapid expansion in the available technology in pulmonary medicine over the last two decades. Although effective application of most of these technologies requires advanced training and therefore utilization by interventional pulmonologists, some have started to make their ways into general pulmonary practice due to their practical indication and relative ease of use. A prime example is endobronchial ultrasound (EBUS), a technology that allows the real-time guidance of mediastinal lymph node sampling with an average sensitivity and specificity of 93% and 100%, respectively. As the benefit of EBUS-guided TBNA over conventional TBNA in many patients has become clearer, the demand for training, both in fellowship programs and for established clinicians, has continued to increase. Beyond bronchoscopy skills and core knowledge of airway and mediastinal anatomy, working with an EBUS bronchoscope requires the acquisition of specific skills, including driving the scope with reduced optics and an oblique angle of view, acquiring and interpreting the ultrasound images, understanding how to operate the equipment and the needle, and performing the TBNA. A virtual reality simulator with a

view mimicking the EBUS bronchoscope would be successful in teaching novice operators to handle the scope effectively and learn the anatomical relationship between airways and surrounding vessels and nodes. Recently, an EBUS capability was added to one of the available bronch simulators (CAE Healthcare, Montreal, Quebec, Canada). Though it has not yet been validated, it holds promise in providing clinicians with a realistic training experience. Alternatively, a lo-fidelity inanimate airway model could serve a similar purpose if simulators are not available. One available airway model (Olympus Inc., Center Valley, Pennsylvania, USA) has a tubular structure with surrounding silicone balls, simulating lymph nodes and allowing a realistic tactile feeling of how the EBUS scope and needle operate. Interpretation of ultrasound images could be learned using computer-based tutorials based on an atlas of CT and ultrasound images. Learning to obtain clear ultrasound images presents additional challenges, as simulators may be unable to mimic real-life challenges of an actual procedure.

An additional essential step for the success in bringing EBUS technology to an institution is adequate training of the staff in the bronchoscopy suite to learn the operation of this new equipment. After they have gained competence in individual skills required to fulfill their role in the procedure, a simulation-based team training exercise should ideally take place in order to optimize teamwork performance and to integrate the dynamic atmosphere of the bronchoscopy suite.

In summary, lo- and hi-fidelity simulation can play an essential role in the learning of new skills among trainees and established physicians before performing procedures in a patient-care setting.

Simulation for Maintenance and Acquisition of Skills for Practicing Chest Physicians

Most of the studies done on simulation and bronchoscopy relate to the teaching for novice learners. However, practicing physicians often encounter important training issues relating to the need to obtain hospital credentialing, maintain learned skills on an annual basis, and learn new procedures.

The ultimate goals of a credentialing process are proper procedure utilization and the delivery of high-quality patient care. This process is currently the responsibility of each health-care facility in the United States; professional societies usually issue consensus-based general recommendations that aid hospitals in this process. An example is the privileging and credentialing criteria for endoscopy and colonoscopy issued by the gastroenterology and surgical societies. In 2003, the American College of Chest Physicians (ACCP) published guidelines for minimal numbers for interventional pulmonary procedures. For example, 25 procedures were needed to establish competency in TBNA, and 10 annual procedures were recommended to maintain competency. These guidelines are based on experts' opinions and not on scientific data evaluating variations in individual performance or patients' outcomes.

A more challenging issue is the learning of a new medical procedure once out of training. The last decade has seen a rapid expansion in procedures available to chest physicians from percutaneous tracheostomy to endobronchial ultrasound and navigation bronchoscopy. The venues for learning such new skills are limited and challenging. Physicians can acquire basic skills through focused courses with didactic and hands-on sessions that can provide the foundation of knowledge and basic skills for such a new procedure. Afterward, physicians can further enhance their skills by taking short sabbaticals in centers performing a high volume of the procedure, seeking proctorship from physicians who perform the procedure or a variation of it (gastroenterologists who perform esophageal ultrasound), or inviting experienced operators to supervise their performance. Clearly, none of these choices are easy to pursue, and there are numerous legal and administrative obstacles that prevent physicians from pursing supervised training in other medical institutions.

Simulation can play a valuable role in the education of practicing physicians. New skills can be learned on the simulator to speed up the learning curve and avoid practice on patients. Performance on existing procedures can be evaluated and corrected on a periodic basis to maintain certification. Before this becomes a reality in our medical practice, more studies are needed to validate the effectiveness of simulation technology in establishing performance metrics and aiding in the certification process, particularly for more complex procedures.

Current Issues with Simulation

Despite the abundance of evidence of the effectiveness of simulation in medical training, the adoption of such as tool in the medical community has been slow.

The first barrier is cost; the currently available hi-fidelity simulators for bronchoscopy are priced over $100,000. This makes the investment in such an educational tool an institutional decision and is subject to budgetary restrictions. It is hoped that the price of this technology will go down with time and increasing competition. Lo-fidelity simulation can offer a cheaper advantage but lacks interaction and feedback capabilities as summarized above.

The second barrier is the lack of research on the effectiveness of bronchoscopy simulation in transferring skills to the bedside and having an impact on patient's outcome. The study by Wahidi et al. in 2010 showed that simulation enhanced the

speed of bronchoscopy skill acquisition performed by trainees on patients; however, the impact on patient's outcome was not studied. Further studies are needed to establish this virtue of medical simulation in bronchoscopy.

The third barrier is the attitude among educators and physicians regarding simulation as a teaching tool. There is still some attachment to the apprenticeship model and doubts about the benefit of simulation. Further research and education about the benefits of simulation will continue to erode into these beliefs and help make simulation an integral part of bronchoscopy education.

Summary

Bronchoscopy is a procedure central to the chest physician's armamentarium to diagnose and treat respiratory diseases. The apprenticeship model remains the major teaching method for bronchoscopy. Though clearly individual interaction with faculty represents a valuable experience in bronchoscopy and procedural education in general, innovative methods are necessary to ensure clinical competency for trainees and delivery of high-quality medical care. There is a mounting body of evidence that simulation-based training can enhance the speed of acquisition of bronchoscopy skills and provide a safe environment for structured training that is acquired away from patients and transferred to the bedside. Not only can simulation help medial trainees but can also play a vital role in the continued education of practicing chest physicians as it relates to maintenance of learned skills and acquisition of new skills in technology that can tremendously improve their patient care.

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Principles of Cancer Staging

12

Paul Baas

Background

Worldwide, approximately 1.3 million persons will be diagnosed with lung cancer each year (WHO 2008). Of these, not more than 15% will survive for 5 years or longer. Although cessation of smoking is the most effective approach to solve this problem, it is not expected that in the near future, the incidence of lung cancer will diminish. Smoking cessation programs may be offered in the Western world; the real threat lies in the less-developed nations and countries with booming economies like China.

For those patients presenting with lung cancer, various treatment modalities are available. The methods available and used most are surgery, radiation therapy, and chemotherapy. Although each method can lead to cure, the toxicity profile varies considerably. Currently, a combination of two or three modalities is proposed to patients.

Lung cancer can be roughly divided into three groups: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and a remaining group that is not smoking related. The incidence of NSCLC is 75%, and for SCLC, it is 15%. NSCLC can be subdivided into adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or not otherwise specified (NOS). The growth pattern of these various types is slightly different, and also the response to treatment varies.

In order to make advances in the treatment of cancer and to communicate optimally between different centers, there is a need for a standard nomenclature. Patients with lung cancer vary in a number of factors with respect to biological behavior, comorbidity, age and performance, and extent of disease. Staging is one of the methods to group patients who have a more or less similar prognosis. Correct description of the other factors of the patient and his or her disease and a proper (randomized) study execution will allow scientists to value reported findings and to select the best treatment for each patient. Stage grouping can thus be seen as one of the approaches to narrow down the optimal treatment approaches for a typical patient.

The first attempt to stage patients was made in the 1940s in France. Later, Mountain based the first TNM staging system on the data of 2,155 patients of the MD Anderson hospital in Texas. This initiative was subsequently adopted by both the AJCC (American Joint Committee on Cancer) and UICC (Union Internationale Contre le Cancer-International Union for Cancer Control) and resulted in a uniform classification in 1987. Since then, the TNM system was updated on a regular basis, incorporating data of more patients. Initially, only a minority of patients from the Middle and Far East and Europe were included. In the last decade, a great effort has been undertaken by the International Association on the Study of Lung Cancer (IASLC) to update and expand the database of the TNM system. This effort resulted in the seventh edition of the stage classification and is based on data from >20 countries contributing to a total of 67,725 patients with NSCLC and 13,290 patients with SCLC (Fig. 12.1).

Clinical Staging

Clinical staging is the process of determining the extent of the disease by using limited invasive procedures and anatomical landmarks, excluding aspects of the biological behavior of the disease or patient characteristics. It comprises of a tumor or T status, a lymph node or N status, and the presence of metastases or M status. After finalizing the required examinations, the clinical staging will be noted as a cTxNxMx. It must be noted that clinical staging is not as accurate as the final pathological staging, which is indicated as a pTxNxMx. In addition, an interim staging after induction chemo- and radiotherapy will be indicated by yTxNxMx.

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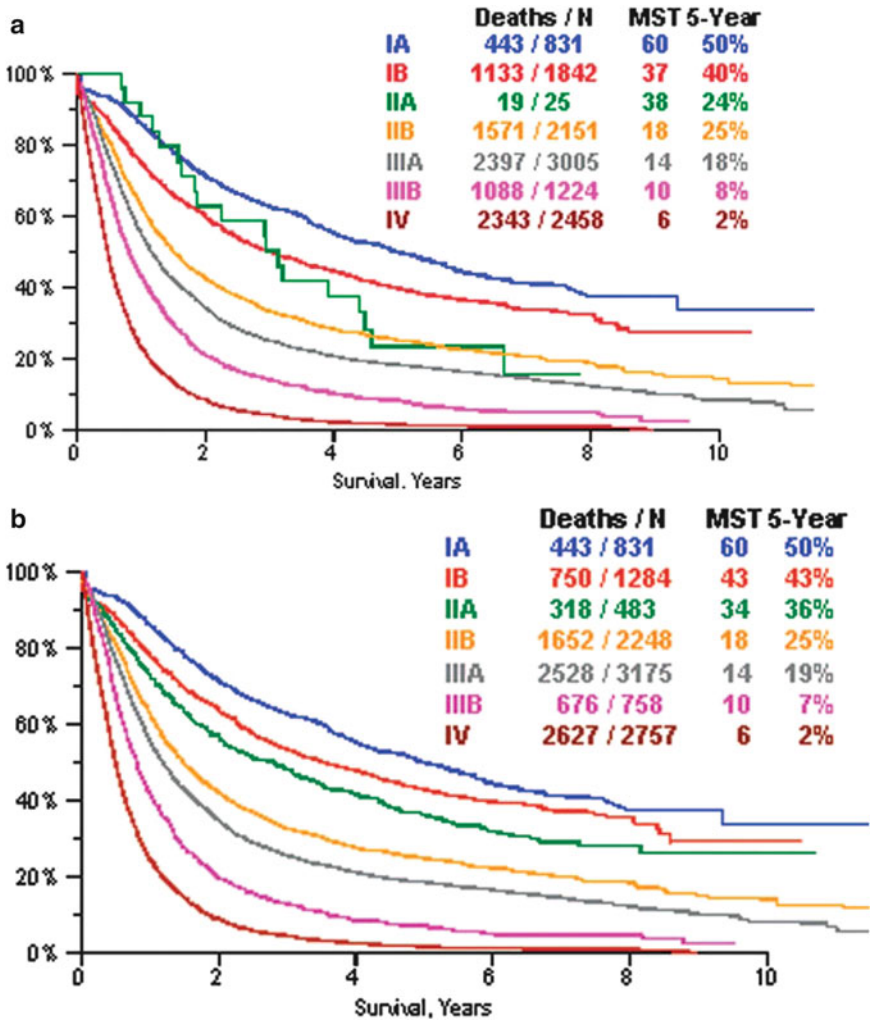

Fig. 12.1 Survival curves according to the seventh IASLC staging system. In *panel A*, the survival figures for the different clinical stages are presented. In *panel B*, the same survival curves are presented but now for the pathological staging. There is a clear difference between the number of stages IB and IIA between the clinical and pathological stages, indicating that imaging techniques in these two groups are often difficult (From The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumours. Peter Goldstraw, FRCS,* John Crowley, Ph.D.,† Kari Chansky, MS,† Dorothy J. Giroux, M.Sc.,†Patti A. Groome, Ph.D.,‡ Ramon Rami-Porta, M.D.,§ Pieter E. Postmus, Ph.D., Valerie Rusch, M.D., and Leslie Sobin, M.D.,# on behalf of the International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. Reprinted with permission from Wolters Kluwer)

Clinical staging consists of the following procedures: physical examination, radiological examination, nuclear medicine examination, endoscopic investigations, and limited surgical interventions.

Physical Examination

The first step in staging is to examine the patient and find signs or symptoms that indicate local or distant dissemination of the disease. Findings during the physical examination will also be of help to plan the next steps. This will avoid examinations that will not contribute to the staging process and finally shorten the time between presentation and start of treatment. Signs of collateral blood flow and elevated central venous pressure will urge the physician to order vascular contrast examinations, sometimes combined with placement of an expandable vascular stent. The appearance of enlarged lymph nodes in the supraclavicular region will indicate at least an N3 status. Signs of Horners' syndrome (unilateral ptosis, myosis, enophthalmus, and reduced sweating) or pain in one shoulder or arm indicates involvement of the cervical plexus by invasion of the tumor. A low position of the diaphragm or reversed movement during respiration is indicative of severe COPD or involvement of the phrenic nerve. Diminished breath sounds and dullness at percussion are indicators of pleural effusion, atelectases, or consolidation of a part of the lung. The appearance of lymph nodes in the axilla or subcutaneous metastases will upstage the patient to stage IV disease when malignant cells are found at fine-needle biopsy. Additional CT or PET scans can be omitted in these cases.

Clinical signs of cyanosis, weight loss, paraneoplastic syndromes, comorbidities, low-performance status, medication use, and the psychological condition of the patient are important factors in the process of final treatment planning.

Radiological Examinations

Information obtained from a standard *chest X-ray* (PA and lateral view) will be the first step in imaging studies. Localization of the primary disease and presence of atelectases or pleural effusion will help to decide on the next investigation. Although less frequently used nowadays, *fluoroscopy* can be of help to identify superimposed lesions, pleural lesions, a reversed movement of the diaphragm, or stenosis of one of the central airways by movement of the mediastinum during forced inspiration.

Computed tomography is the examination of choice to determine the anatomical landmarks of the tumor and to obtain information about any possible mediastinal lymph node involvement. The extent of the primary tumor can be determined, and the size of the tumor can be measured. Not always a clear discrimination can be made between actual growth into surrounding tissues, as is shown in Fig. 12.2. The appearance of post-obstructive pneumonia or atelectasis can also negatively influence the measurement. Sometimes a PET scan (see below) can be of help. For discrimination of the lymph nodes in the hilar and mediastinal region, contrast-enhanced scans are a requisite. The currently available CT scans are fast and have a high resolution that allows multiplane viewing. Coronal and sagittal images can be constructed in addition to the axial recordings and help to determine whether the primary tumor is invading the mediastinum or other vital structures (Fig. 12.3).

In the following figures, examples of different stages with the plotted anatomical/radiological landmarks are presented.

Positron emission tomography is considered a standard examination for the staging of the early stages of NSCLC. Using fluorodeoxyglucose (FDG), the scan can identify metabolic processes in the body. This tool can discriminate

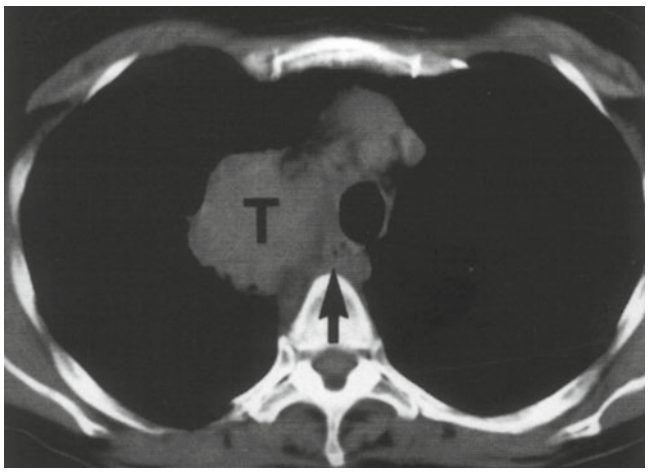

Fig. 12.2 Axial CT image of a patient with NSCLC. The tumor is located adjacent to the mediastinum. Although there is an indication that the more ventral part of the tumor (T) is probably growing into the mediastinum, the more dorsal part might be separate. The arrow indicates the location of the esophagus. This tumor is graded as minimally a T3 based on the CT image alone. Additional EUS and EBUS examination can be used to better visualize the local situation

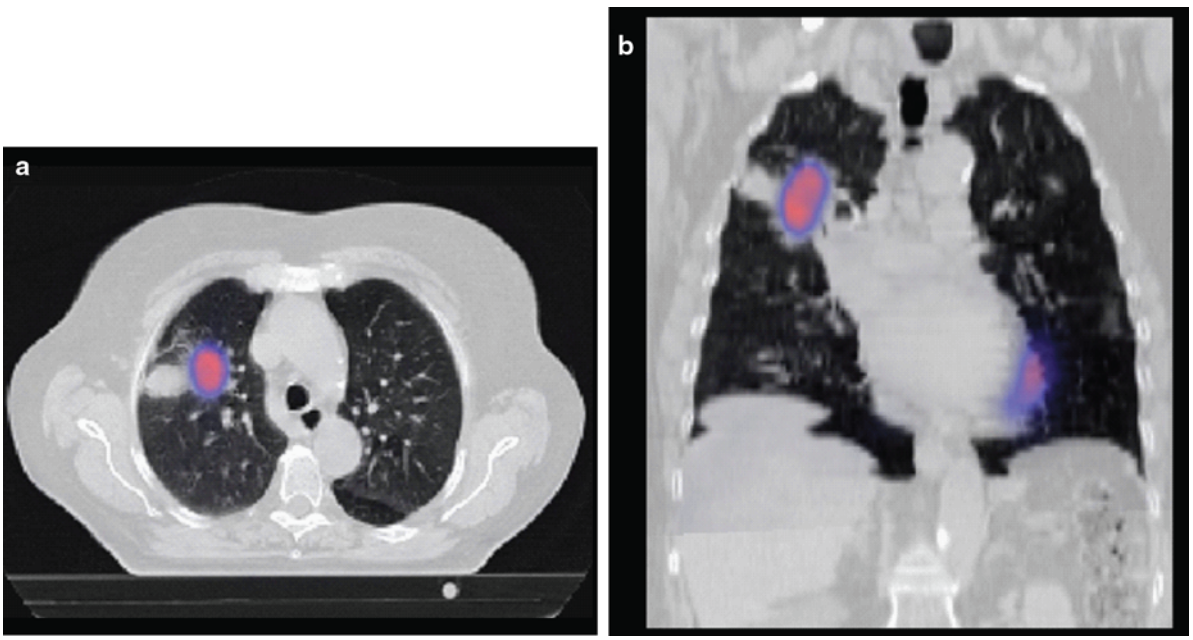

Fig. 12.3 Combination of PET and CT scans using fusion techniques. The CT and PET are made on the same time and corrected for anatomical variation in position of the patient. The axial and coronal images show a tumor-avid lesion in the anterolateral part of the *right upper* lobe (RUL). The CT scan shows a PET negative extension that is due to post obstruction atelectasis. Some physiologic activity of the myocardium is visible

Table 12.1 Causes of false-positive and false-negative PET

False positive	False negative
Talc pleurodesis (up to 4 months after procedure)	Hyperglycemia
Sarcoidosis	Tumor is not FDG avid
Rheumatoid arthritis	Too long interval after FDG injection
Wegeners' granulomatosis	Small size (<8 mm)
Chronic lymphatic disorders	Carcinoid tumors
Infectious (pneumonia, abscess, fungal, mycobacterial)	Ground-glass appearance of tumor (previously known as bronchioloalveolar cell carcinoma)
Radiation pneumonitis/esophagitis	
Invasive procedures	
Benign tumors (Warthin's' tumor, colonic polyps, adrenal adenomas)	

Table 12.2 Accuracy of combined PET-CT scanning for lung cancer. In the older studies, the CT scan was performed separately from the PET scan resulting in less accurate matching

PET-CT scan	Year	Number of patients	Accuracy (%)	Reference
T-stage	2003	50	88	Lardinois
	2004	129	64	Cerfolio
	2005	36	97	Halpern
	2007	50	86	De Wever
N-stage	2003	50	81	Lardinois
	2004	129	78	Cerfolio
	2005	36	78	Halpern
	2007	50	84	De Wever

between processes that have a high, low, or absent metabolic activity. When the primary tumor is FDG avid, the sensitivity to detect malignant lymph nodes or distant metastases is very high. The PET scan cannot be interpreted reliably when the primary tumor is not FDG positive or in case of a concurrent infection or other causes (Table 12.1). Concurrent infections occur often in patients with central obstruction by the tumor or due to COPD. Sarcoidosis is one of the well-known diseases that have a high FDG uptake and can mimic a tumor or positive lymph nodes. Therefore, it is important to obtain proof of one of the involved lymph nodes or lesions found in distant sites. The PET scan is not informative on the presence of ingrowth into other structures like the mediastinum when the primary tumor is centrally located. The modern scans combine CT and PET and allow projecting both images on top of each other (Fig. 12.3 and Table 12.2), enabling the physicians to decide on the further diagnostic steps (Fig. 12.4). The combination of CT scan lymph node size and PET activity improves the sensitivity and specificity.

Endoscopic Investigations

These investigations are described in other chapters of this book. Standard procedures like bronchoscopic examination with or without fluoroscopy are the basis for the diagnosis and appreciation of endobronchial extension.

In the current work-up of the mediastinum in patients with NSCLC, the indication for mediastinoscopy has declined because of the reliability and safety of the endobronchial techniques. Endobronchial ultrasound (EBUS) and endoesophageal ultrasound techniques (EUS) are now readily available, and most cancer centers and university clinics now have experienced staff. Mediastinoscopy can therefore be reserved for special cases or for the evaluation of the mediastinum after induction therapy.

Surgical Staging

Surgical procedures in the staging process can be subdivided into *mediastinoscopy*, *thoracoscopy*, *and exploratory thoracotomy*. In the case of mediastinoscopy, it has already been discussed that the indication has been reduced since the introduction of EBUS and EUS. Even for the lymph node stations in the aortopulmonary window, the need for a parasternal mediastinoscopy has been reduced. Cervical and para-mediastinal mediastinoscopy are merely indicated when the endobronchial ultrasound examination was not representative or available or when a larger tumor specimen is required. The need for more histology specimen is now indicated in the case of studies or when first line treatment with targeted biologicals is planned.

A thoracoscopic examination has limited indications in the primary staging process. In the case of a presentation with pleural lesions and effusion, at least two separate pleural fluid specimens must be examined at the cytology department. When returned negative or in case of a dry tap, a thoracoscopy can be indicated to prevent a futile thoracotomy. In some cases, a thoracoscopy can be indicated because of the need for histology or as part of specific study requirements. In some countries, pulmonologists perform medical thoracoscopies for inspection of the pleural cavity, to evacuate the fluid, to take pleural biopsies, or even to perform a pleurodesis. In other cases, a video-assisted thoracoscopy (VATS) is performed in the operating room with optimal sedation of the patient. This examination is typically performed by the thoracic surgeon or in specialized centers by the pulmonologist.

In selected cases, a thoracotomy is performed for means of both staging and resection. These cases are cases in which no diagnosis could be obtained by other means or when the tumor lies adjacent to the mediastinum and ingrowth is considered unlikely. These indications are becoming less frequent as a result of the implementation of EUS and transthoracic fine-needle aspiration.

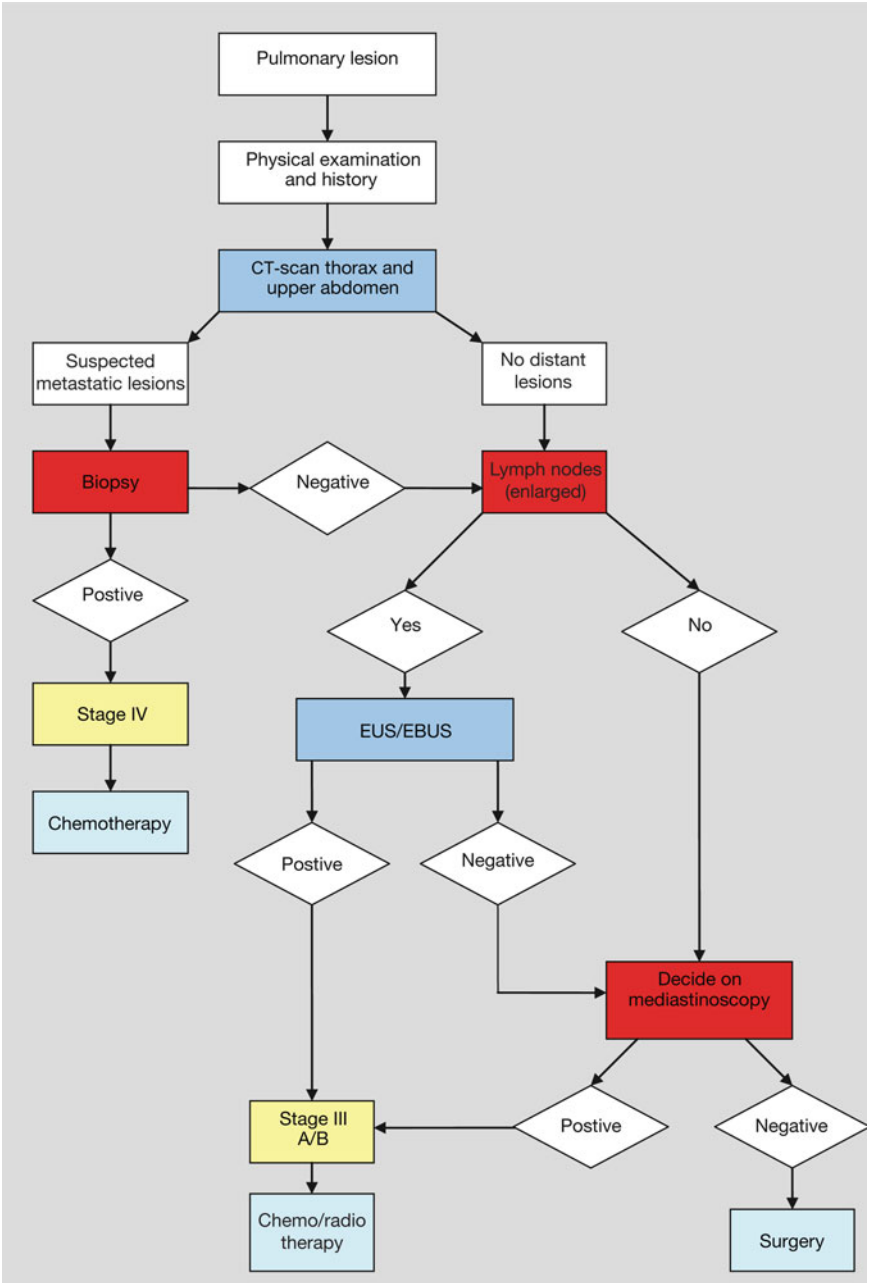

Fig. 12.4 Decision-making tree of patients presenting with a pulmonary lesion with a high level of suspicion for lung cancer

TNM Classification

Staging is considered to be one of the backbones in designing an optimal treatment in lung cancer. With proper staging, it is possible to select the best treatment and to compare studies from different centers.

In the last few years, the TNM classification has undergone significant changes. Based on a worldwide initiative of the IASLC (International Association on the Study of Lung Cancer), 19 countries included data on 67,725 patients with NSCLC in the period of 1990–2000. This effort resulted in the seventh international staging system and is now widely used since January 1, 2009. The suggestions made included additional cutoffs for tumor size, with tumors >7 cm moving from T2 to T3, to reassign the category given to additional pulmonary nodules in some locations, and finally reclassifying malignant pleural effusion as an M descriptor. This has resulted in the new staging and grouping system, as shown in Tables 12.3 and 12.4.

Recommendations

The principles of staging have undergone important changes over the last few years. Besides the introduction of the PET-CT scan, the more recent availability of endoscopic

Table 12.3 Staging of primary tumor, lymph nodes, and metastases according to the seventh edition of the IASLC staging system (adapted from the seveth IASLC staging system)

Tx	Tumor cells detected in sputum or bronchial washings: primary tumor cannot be assessed by radiology or bronchoscopic examination
T0	No evidence of the primary tumor
Tis	Carcinoma in situ
T1	Greatest size ≤3 cm, beyond main bronchus, not invading visceral pleura
	Superficial growing tumor which is of any size but limited to the bronchial wall and may extend into the main bronchus
T1a	Tumor ≤2 cm greatest diameter
T1b	Tumor >2 cm but ≤3 cm
T2	Tumor > 3 cm but ≤ 7 cm or tumors with any of the following aspects: invasion of the visceral pleura, located in the main bronchus but ≥2 cm of the main carina, associated with atelectasis or obstructive pneumonia which extends the lobe but does not involve the whole lung
T2a	Tumor >3 cm but ≤5 cm
T2b	Tumor >5 cm but ≤7 cm
T3	Tumor >7 cm or involvement of chest wall (including sulcus superior tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, within 2 cm of the main carina (but no involvement of the carina), atelectasis or obstructive pneumonia of the whole lung, separate tumor nodules in the same lobe
T4	Tumor of any size that invades the major organs, involvement of the main carina, vertebral bodies, recurrent laryngeal nerve, tumor nodule(s) in a different lobe
Nx	Regional lymph nodes cannot be assessed
N0	No involvement of regional lymph nodes
N1	Metastases in the ipsilateral peribronchial hilar lymph nodes or intrapulmonary lymph nodes. No differentiation is made between direct extension and metastases
N2	Metastases in the ipsilateral mediastinal lymph nodes and/or subcarinal lymph nodes
N3	Metastases in the contralateral mediastinal, contralateral hilar lymph nodes. Metastases in the ipsi- or contralateral supraclavicular or scalene lymph nodes
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Presence of distant metastases
M1a	Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastases

Table 12.4 Stage grouping according to the seventh edition of the IASLC staging system (adapted from the seventh IASLC staging system)

N status				
T status	N0	N1	N2	N3
T1a	IA	IIA	IIIA	IIIB
T1b	IA	IIA	IIIA	IIIB
T2a	IB	IIA	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIB
T4	IIIA	IIIA	IIIB	IIIB
M1a	IV	IV	IV	IV
M1b	IV	IV	IV	IV

techniques has improved the pretreatment diagnosis of mediastinal involvement in patients with NSCLC. Currently, the use of the seventh edition of the staging system by the IASLC is mandatory to optimally stage patients. The optimal treatment choice, however, does not solely depend on the stage but should also take into account patient characteristics like performance, comorbidity, and psychological status. For a general approach, the decision tree in Fig. 12.4 can be used.

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Part II

Bronchoscopy, Section 1: Diagnostic Procedures

Laryngoscopy

13

Ulrich Goessler

Clinical Anatomy

The larynx is a multitask organ playing distinct roles in breathing, swallowing, vocalization, protection of the airway, and building pressure during heavy lifting and defecation. The multifunction purpose of the larynx is reflected by a stringent relationship between morphology and function as well as a highly organized neural control with specialized tissue adaptions.

Cartilages, Ligaments, Membranes, Spaces

The most important components of the laryngeal skeleton are five cartilages (epiglottis, thyroid cartilage, cricoid cartilage, two arytenoid cartilages) and one bone (hyoid bone). These structures are attached to the skull base and the mandible and are kept in place by a network of ligaments and joints, allowing changes in distance and angles of these structures.

The *thyroid cartilage* is composed of hyaline cartilage, forms the Adam's apple (angle between thyroid laminae 120 ° in women, 90 ° in men), and begins to ossify around 20 years of age. Inferiorly, the thyroid cartilage conjoins with the cricoid cartilage via a synovial joint, around allowing rotation a transverse axis passing through both joints. The thyroid cartilage is covered by perichondrium, which is thinner internally. The *cricoid cartilage* is the only circular rigid narrowing of the upper aerodigestive tract. The anterior aspect of the signet-shaped cartilage is thinner and also ossifies later than the posterior aspect; it is more susceptible to fracture during surgical manipulation. Connection to the thyroid cartilage occurs via the cricothyroid membrane and the cricothyroid ligament. The internal diameter is smallest in the frontal plane and averages 11.6 mm in women and about 15 mm in men; this should be kept in mind with regard to tracheal intubation, dilation, stenting, and endoscopy or anastomosis.

The *arytenoid cartilages* are the principal moving parts of the larynx, performing a combined movement (rocking, gliding, and rotation) to approximate to the midline. Cranially, there are located two small cartilages, the corniculate (Santorini) and cuneiform (Wrisberg) cartilages.

The *epiglottis* is composed of fibroelastic cartilage and forms a leaflike structure in the supraglottis which is attached to the thyroid cartilage by the petiolus immediately below the thyroid notch by the thyroepiglottic ligament. The hyoepiglottic ligament is a connection between the hyoid bone and the lingual surface of the epiglottis. The epiglottis is covered by perichondrium, which is less intensely adherent on the lingual surface. This is the reason for epiglottic edema to be more prominent on the lingual surface.

The *vallecula* is a pocket formed by the base of the tongue and the epiglottis. The *aryepiglottic folds* span the distance between the sides of the epiglottis and the arytenoids; they form a wall that separates the larynx from the pyriform sinus.

Muscles and Innervation

The *extrinsic depressors* (sternohyoid, sternothyroid, thyrohyoid, and omohyoid) are innervated by the ansa cervicalis (C1–C3); the *extrinsic elevators* are as follows: geniohyoid (C1), digastric (venter anterior CN V, venter posterior CN VII), mylohyoid (CN V), and stylohyoid (CN VII).

The *posterior cricoarytenoid* (PCA) muscle is the sole abductor and is innervated by the recurrent laryngeal nerve. The *lateral cricoarytenoid* (LCA) muscle is responsible for vocal fold adduction and is innervated by the recurrent laryngeal nerve. The *thyroarytenoid* (TA) muscle increases

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vocal fold tension and adducts the vocal folds. The medial aspect of the TA is called the *vocalis* muscle. The *interarytenoid muscle* is the only unpaired muscle, adducts the vocal folds, and is innervated by the recurrent laryngeal nerve. The only muscle that is innervated by the external branch of the superior laryngeal nerve (SLN) is the *cricothyroid*; it is responsible for adduction and increases the vocal fold tension and length; thus, it is the chief pitch-changing muscle.

Arytenoid Movement

The complex arytenoid motions occur in three directions. The main movement occurs along an anterior to posterior and a vertical axis and is described as revolving, rocking, or pitch-like motion along the minor axis of the cricoid's elliptically shaped facet.

Laryngoscopy

Indirect Laryngoscopy

Without opening of the larynx, procedures (biopsy, polypotomies, swab, etc.) may be performed using a mirror or an endoscope (flexible via the transnasal route or rigid 70 ° or 90 ° scope via the transoral route under local anesthesia, indirect laryngoscopy) (Fig. 13.1). Contraindications include an extreme gagging reflex, anatomically compromised vision, lesions in the anterior commissure as they may just be out of instrument range, broad-based lesions (e.g., Reinke's edema, leukoplakias), and children younger than 14 years as they may not provide the necessary compliance.

Before the procedure, local anesthesia with tetracaine (Pontocaine) 2% or lidocaine 4% with addition of Adrenalin is applied. If the transnasal route is used, a nasal decongestant with local anesthetic (e.g., xylometazoline with lidocaine) is highly recommended, if the transoral route is used, oral cavity, pharynx, and laryngeal mucosa are sprayed step by step; the larynx is then brushed with an arcuated cotton-bearing hook under indirect vision. With extreme gagging, infiltration anesthesia of the cranial recurrent nerve may be performed from outside, and infiltration of the glossopharyngeal nerve at the posterior inferior pole of the tonsil with 2 cc of 1% lidocaine may be necessary. Cocaine is effective in cases of inadequate action of other local anesthetics and is tolerated well by the laryngeal mucosa. The patient is usually sitting upright. Special instruments, such as an arcuated cotton-bearing hook, epiglottic hook (Reinhardt), cutting forceps, binocular microscope, or laryngoscope, may be used.

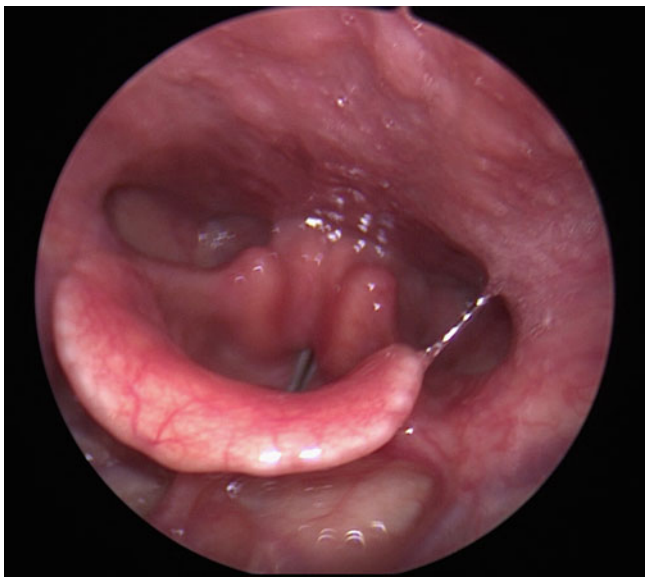

Fig. 13.1 View of the larynx as provided by the 70 ° rigid scope

Visualization should follow a standardized pattern as to guarantee inspection of all regions of the larynx. Inspection starts at the tongue base bilaterally, then the valleculae and epiglottis are inspected. The aryepiglottic folds are followed posteriorly, then the arytenoid cartilages are inspected. Attention is now directed toward the glottis: The false vocal cords, the sinus, and the true vocal cords are inspected during respiration and phonation. During respiration, the subglottic space can be visualized. Indirect laryngoscopy offers only limited view of the piriform sinus and the postcricoid region. These regions can only be properly visualized by direct laryngoscopy under general anesthesia.

Follow-up after surgery may include voice rest for 3–7 days and abstinence from smoking and alcohol. First food ingestion may occur 2 h after surgery. Inhalation (e.g., dexpanthenol) may ease a feeling of dryness and sore throat. If needed, antibiotic coverage and medical suppression of cough for 3 days may be used. If the patient is prone to edema or has a narrow glottic opening, monitoring and corticosteroids may be necessary.

Risks and complications include hoarseness (due to tissue defects, vocal cord trauma, scarring of the vocal cords, or formation of synechias) and laryngeal edema with dyspnea.

Patient and surgeon should be relaxed and calm. Scopes and instruments may be handled more easily, if the surgeon's upper arms are supported by his thorax. A tremorous hand as well as a nervous patient may lead to defective excision and damage of the larynx. Before the excision, the patient should take a couple of deep breaths in order to allow the larynx to stay still during prolonged inspiration.

Advantages of the indirect laryngoscopy comprise the cost-effectiveness with no need of general anesthesia, no

need of assistance and outpatient procedure, and no need of costly equipment. The disadvantages are the limited indications and practicality, the limitation to the use of one hand, lack of precision, and dependence on the patient's cooperation.

Direct Rigid Laryngoscopy

Direct vision (direct laryngoscopy) offers the advantage of three-dimensional appreciation of the larynx, bimanual instrumentation, application of tools such as the laser, and clear visualization of "hidden" regions such as the piriform sinus and the postcricoid region. Due to the usage of a rigid scope, general anesthesia is mandatory. Rigid laryngoscopy is mostly part of a so-called panendoscopy including a flexible or rigid bronchoscopy and a flexible or rigid esophagoscopy.

Preoperative management includes proper documentation of the pathology in question and the status quo of laryngeal anatomy and physiology, preferably by videostroboscopy (Table 13.1). Management by anesthesia requires atraumatic intubation with a small endotracheal tube, typically a 5.0 tube. Most cases can be managed with the endotracheal tube in place. If necessary, jet ventilation can be used. Directly at the end of surgery, application of 4% lidocaine is prudent to minimize the risk of laryngospasm after extubation.

Different rigid laryngoscopes are available (Kleinsasser laryngoscope, Boston, Dedo, Ossoff, Zeitels, etc.). Proper positioning of the patient is the first step to good visualization during the procedure. The patient is in supine position, and the neck is extended using a pad under the shoulders and a soft ring under the head to attain stable positioning (Fig. 13.2).

Exposure is key to visualization and proper performance of surgical procedures. Different means of instrumentation (rigid laryngoscopes) are available, all offering excellent exposure Peroral rigid laryngoscopy begins with application of a tooth guard (Fig. 13.3), preferably using soft plastic dental protection with a metal coverage to prevent accidental damage to the teeth. The upper incisors are at greatest risk of injury as they are long and exposed to the rigid instrument. It is extremely important never to use the teeth as a fulcrum. Care is also taken not to injure the lips by pulling them inside with the laryngoscope and lacerating them between the scope and the teeth. Gentle insertion of the laryngoscope with lighting is performed with the left hand in the right-handed surgeon (Fig. 13.4). The right hand is then free for the usage of suction or a grasping instrument to aid proper exposure. Tongue and soft palate including the tonsils are inspected. Next the valleculae, tongue base and the lingual and laryngeal surface of the epiglottis are visualized. The aryepiglottic folds are followed posteriorly to visualize the arytenoid cartilages. The piriform sinus is inspected bilaterally. The endotracheal tube is then pushed anteriorly, and the postcricoid area is inspected thoroughly. The laryngoscope is used to lift the tip of the epiglottis. This so-called "engagement" of the epiglottis is necessary to gain clear visualization and access to the larynx. Now the attention is turned toward the larynx and the microscope is used for the following part of the procedure (Fig. 13.5). Proper inspection is performed including the false and true vocal cords; the ventriculus (sinus of Morgagni) is palpated with a hook. The anterior and posterior commissures are inspected. If the anterior commissure cannot be visualized, gentle cricoid pressure can be applied to maneuver the larynx in the proper position. The laryngoscope is retracted slowly; the tooth guard is removed. Finally, tongue base, floor of the mouth, lateral pharyngeal walls, and the lower part of the nasopharynx are palpated enorally and bimanually, using one finger enorally and the opposite hand from the outside.

Table 13.1 Indications and contraindications for direct/indirect laryngoscopy

Indications for direct laryngoscopy
Persistent hoarseness
Suspected neoplasm
Chronic cough
Chronic postnasal drainage
Recurrent epistaxis
Chronic rhinorrhea
Chronic nasal congestion or obstruction
Hemoptysis
Hemorrhage from throat
Throat pain
Otalgia
Airway obstruction
Dyspnea
Stridor
Dysphagia
Head or neck masses – unknown primary tumor
Laryngeal injury with hoarseness or airway obstruction
Chronic aspiration
Velopharyngeal incompetence
Suspected foreign body
Recurrent serous otitis media in an adult
History of tobacco use
Obstructive sleep apnea or severe snoring
History of thyroid disorders
Anosmia/Hyposmia
Headaches or facial pain
Relative contraindications for direct laryngoscopy
Problems with stiffness of cervical spine
Retrognathia
Trismus

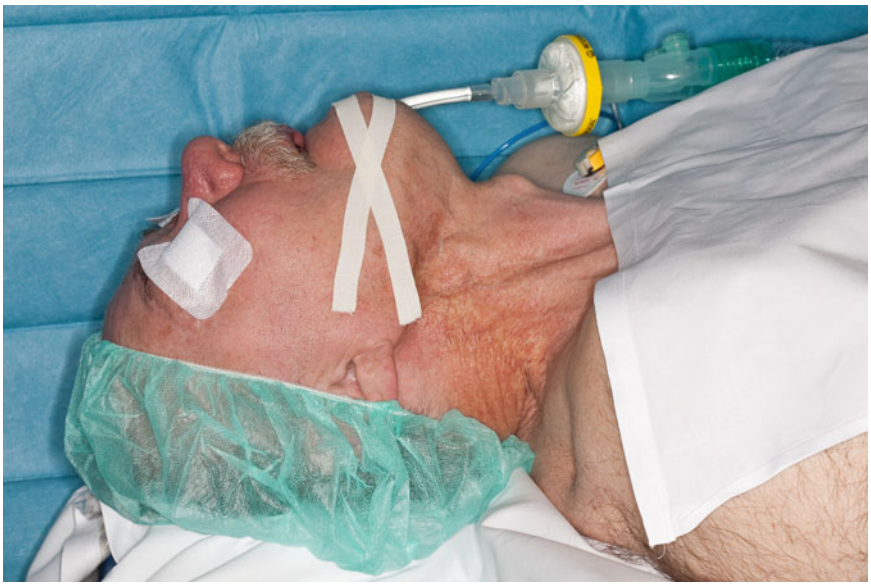

Fig. 13.2 Rigid laryngoscope (Kleinsasser) with included lighting

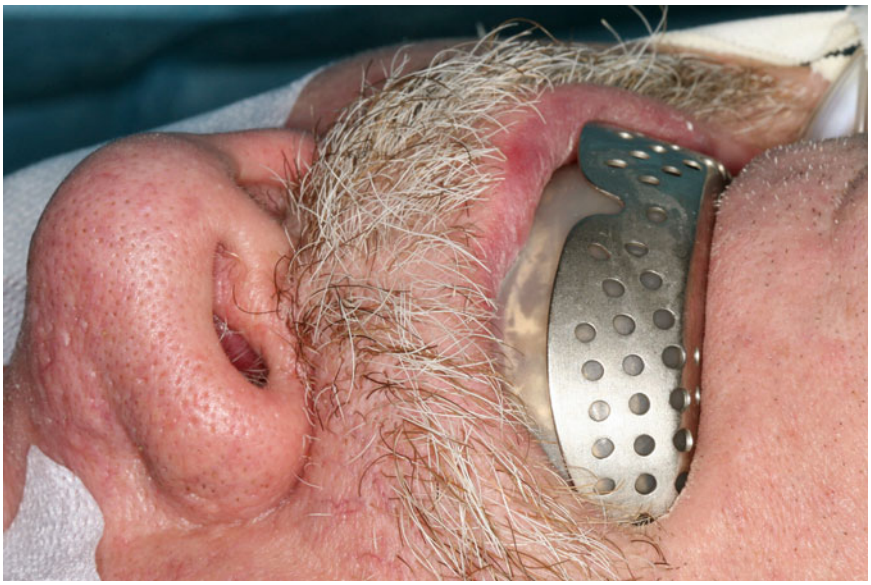

Fig. 13.3 Proper patient positioning

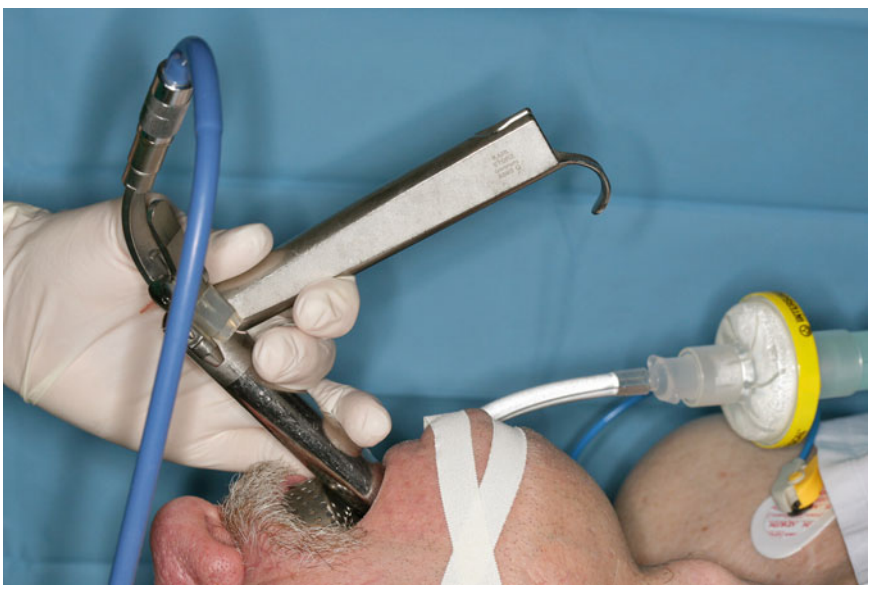

Fig. 13.4 Application of tooth guard and gentle insertion of the laryngoscope

Fig. 13.5 Laryngoscopy in position and view through the microscope

Diagnostic Indications for Direct Laryngoscopy

Dysphonia is the most common symptom that leads to involvement of ear, nose, and throat specialist with the question of laryngeal pathology. Dysphonia is a subjective term that is used to describe perceptual irregularities of the voice. This symptom may be the result of numerous conditions affecting the lungs, the larynx, or the supraglottic airway. A differential diagnosis is summarized in Table 13.2.

Laryngeal causes for hoarseness include vocal cord nodules, polyps, cysts, granulomas, papillomas, hemangiomas, and Reinke's edema.

Vocal fold nodules are defined as localized, benign, and superficial growths on the medial surface of the true vocal folds that are commonly believed the result of phonotrauma. Nodules are bilateral with a classic location at the junction of the anterior and middle third of the vocal fold (i.e., the midpoint of the membranous vocal fold). Nodules are most often observed in women aged 20–50 years, but they are also found commonly in children (more frequently in boys than in girls) who are prone to excessive shouting or screaming.

Vocal fold polyps (Fig. 13.6) are generally unilateral and have a broad spectrum of appearances, from hemorrhagic to edematous, pedunculated to sessile, and gelatinous to hyalinized. Vocal fold polyps are believed to result from phonotrauma; however, they are also recognized to potentially arise from a single episode of hemorrhage.

Vocal fold polyps typically involve the free edge of the vocal fold mucosa, although they may originate along the superior or inferior borders. Both nodules and polyps may interrupt the vibratory patterns of the vocal fold by increasing the mass and reducing the pliability of the overlying cover, as well as by impeding proper closure of the membranous folds.

Table 13.2 Differential diagnosis of dysphonia

*V*ascular (thoracic aneurysm)
*I*nflammation (laryngitis (viral, bacterial, fungal), Reinke's edema)
*N*eoplasm (laryngeal tumor: benign (cysts, polyps, nodules, granulomas, papillomatosis)) or malignant (laryngeal cancer and cancer of the left hilum of the lung) and *n*eurologic (stroke, Guillain Barré, myasthenia gravis, multiple sclerosis)
*D*egenerative (systemic diseases: amyotrophic lateral sclerosis, Parkinson disease)
*I*ntoxication (smoking, alcohol, medications)
*C*ongenital (laryngeal web, glottic stenosis)
*A*llergies (angioedema)
*T*rauma and thyroid surgery (intubation and inhalation injuries, arytenoid dislocation, voice abuse)
*E*ndocrine (hypothyroidism with laryngeal myxedema; adrenal, pituitary, and gonadic disorders; pubescence)

Two types of cysts are found within Reinke's space. Mucus retention cysts are often translucent and are lined with cuboidal or columnar epithelium. Epidermoid cysts contain epithelium or accumulated keratin. These lesions may be true epithelial-lined cysts or pseudocysts.

Laryngeal hemangiomas (Fig. 13.7) in about 90% present within the first 6 months of life. They are usually located in the subglottic space and are capillary in type. Treatment includes corticosteroid therapy, injection with interferon alpha 2, and surgical excision with CO2 laser.

Contact granulomas (Fig. 13.8) of the larynx are benign lesions of the posterior glottis that usually are centered over the tips of the cartilaginous vocal process of the arytenoid

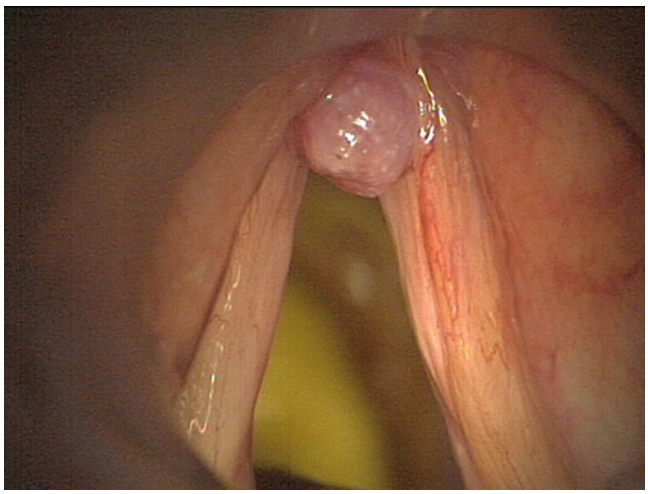

Fig. 13.6 Vocal fold polyp

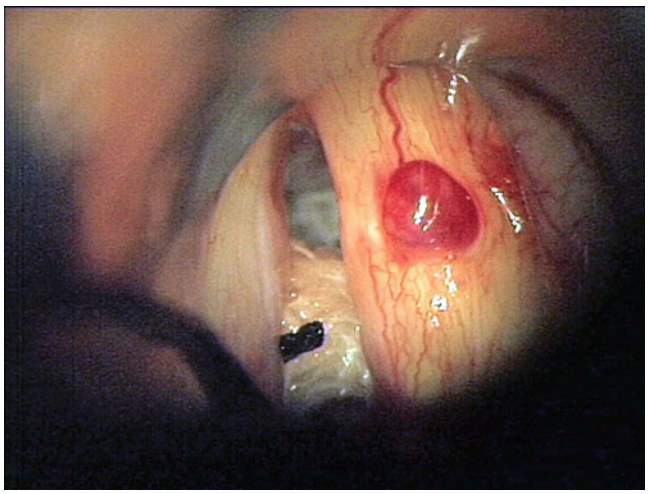

Fig. 13.7 Angioma on right vocal fold prior to laser excision

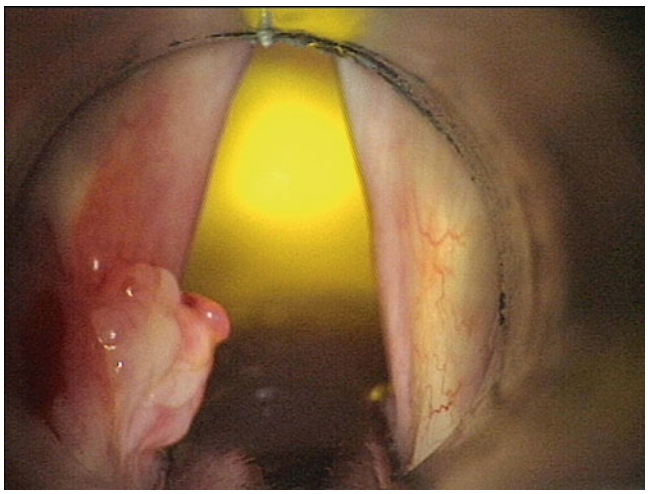

Fig. 13.8 Intubation granuloma on left posterior vocal fold

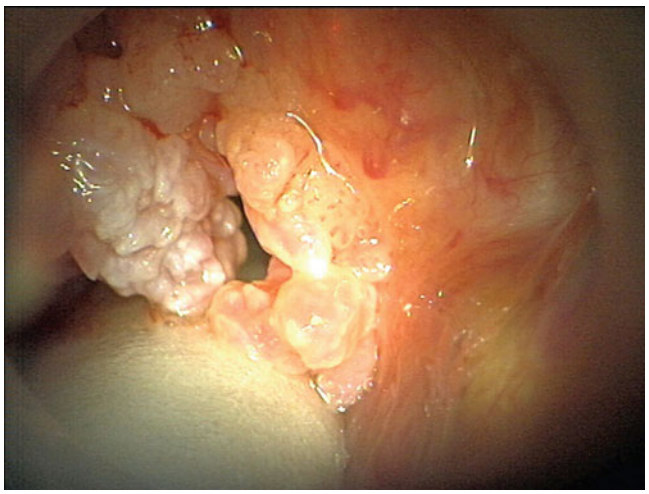

Fig. 13.9 Recurrent laryngeal papillomatosis prior to CO2 laser excision

cartilages. They may be due to vocal trauma, habitual throat clearing, recurrent cough, and intubation trauma.

Laryngeal papillomas (Fig. 13.9) can occur at any age; most commonly, they manifest in childhood between the age of 1 and 3 years. The disease is caused by the human papilloma virus (HPV 6 and 11). Causal treatment does not exist and repeated microsurgical ablations may be necessary, aiming at maintaining an airway and improving voice quality.

Gastroesophageal reflux may lead to a chronic laryngitis with hoarseness and Reinke's edema or polypoid corditis (Fig. 13.10) and causes the vocal folds to bilaterally swell, giving them an uneven, saclike appearance. Individuals with Reinke's edema typically have low-pitched, husky voices. Common causes of Reinke's edema include smoking, gastroesophageal reflux, and hormonal changes such as hypothyroidism and chronic voice abuse.

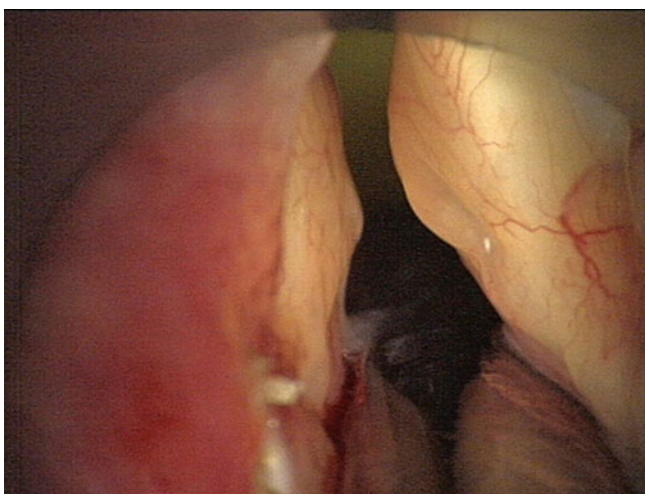

Fig. 13.10 Bilateral Reinke's edema

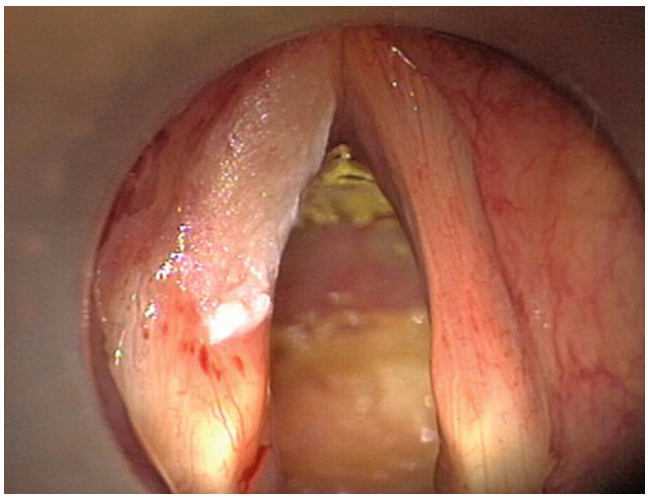

Fig. 13.11 T1 laryngeal carcinoma of left vocal cord prior to CO2 laser excision

Laryngeal cancer (Fig. 13.11) makes up 1–2% of all malignancies worldwide. The incidence of the disease varies greatly from country to country. Tobacco use is the most important and most preventable risk factor for the development of squamous cell carcinoma of the larynx. Smoking tobacco is believed to be a direct cause of up to 95% of glottic and supraglottic carcinomas. Alcohol is an independent risk factor for the development of laryngeal malignancy, increasing the risk up to five times in nonsmokers. More importantly, alcohol has been implicated as a synergistic cofactor when combined with tobacco use. The synergistic risk for smokers who drink is estimated to be 100 times that of individuals who do not smoke or drink. Diet may play a role in both the development and prevention of laryngeal malignancies. A diet deficient in fruits and vegetables can increase the risk of development of laryngeal cancer, while a diet rich in these foods may be preventative. Occupational exposures such as diesel fumes, sulfuric acid, coal dust, and machining fluids have been associated with laryngeal malignancy. About 10% of patients with a malignancy in the upper respiratory tract simultaneously have a second malignancy in the lungs.

Laryngeal malignancy can be classified according to the site: supraglottis, glottis, and subglottis. The supraglottis includes the suprahyoid epiglottis, the infrahyoid epiglottis (most common site), aryepiglottic fold, arytenoids, and false vocal cords, and the inferior border to the glottis is the apex of the ventricle. The glottis includes the true vocal cords and the area 1 cm below the apex of the ventricle. The areas of the glottis are the true vocal cords and the anterior and posterior commissures. The subglottis covers the area from 1 cm below the ventricle to the cricoid cartilage (Table 13.3).

Therapeutic Indications for Direct Laryngoscopy: Removal of Benign Disease (Vocal Cord Nodules, Polyps, Cysts, Granulomas, Papillomas, Hemangiomas, Reinke's Edema) or Malignant Disease (Carcinoma)

For most benign conditions, cold excision procedures are preferable to laser excision methods. To date, microflap surgery is the gold standard due to more favorable healing compared to laser excision (more scarring after laser excision due to fibroblast proliferation and loss of mucosal wave).

The lateral microflap is useful for more challenging laryngeal pathology. The usage of the vocal ligament area lateral to the area of the primary pathology makes identification of surgical landmarks easier. The surgical incision is laterally based and leaves a surgical scar on the superior or lateral surface of the vocal fold. This is advantageous in leaving the epithelium of the free edge intact, reducing the trauma due to pathology removal and thus promoting the healing.

The indications are lesions that result in a loss of the mucosal wave (e.g., cysts) and lesions that might be adherent to the vocal ligament (broad-based vocal fold polyps).

The surgical sequence includes the following steps: inspection and palpation of the lesion gaining information about the ease with which the lesion may be separated from the vocal ligament, inspection of the mucosa overlying the pathology, hemostasis by application of a cottonoid soaked with epinephrine, incision on the superior and lateral aspect of the vocal fold with a sickle knife in a posterior to anterior direction, and elevation of the epithelial flap with a right-angled flap elevator. Dissection occurs in the Reinke's space (superficial lamina propria) superficial to the pathology. Separating the lesion from the epithelium first facilitates further dissection, as separation of the lesion from the vocal ligament offers more resistance than elevation of the flap. Dissection between lesion and vocal ligament is performed using blunt (elevator) and sharp (microscissors) dissection; then, the microflap is redraped into position.

One pathology of the hypopharynx is noteworthy: Zenker's diverticulum is a mucosal herniation arising from the Kilian's dehiscence between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor muscle. Diagnosis is made by history, examination, and gastrografin swallow (lateral oblique film gives best overview). Most diverticula should be treated surgically; though, in some older people with minimal symptoms, a wait-and-see policy may be pursued. The concept of the surgery is to restore direct continuity of pharynx and esophagus; therefore, the septum between esophagus and the diverticulum is dissected in the midline. The mucosal septum consists of the most superior portion of the upper esophageal sphincter. The surgery is performed transorally under general anesthesia.

Table 13.3 TNM classification of laryngeal carcinomas

Primary tumor
Supraglottis
T1: Tumor limited to one subsite* of supraglottis with normal vocal cord mobility
T2: Tumor invades mucosa of more than one adjacent subsite* of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3: Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues
T4: Tumor invades through the thyroid cartilage and/or extends into soft tissues of the neck, thyroid, and/or esophagus
Glottis
T1: Tumor limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a: Tumor limited to one vocal cord
T1b: Tumor involves both vocal cords
T2: Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
T3: Tumor limited to the larynx with vocal cord fixation
T4: Tumor invades through the thyroid cartilage and/or to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, pharynx)
Subglottis
T1: Tumor limited to the subglottis
T2: Tumor extends to vocal cord(s) with normal or impaired mobility
T3: Tumor limited to larynx with vocal cord fixation
T4: Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, esophagus)
Regional lymph nodes
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a: Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3: Metastasis in a lymph node more than 6 cm in greatest dimension

Source: Wittekind C, Klimpfinger M, Sobin LH. TNM-Atlas: illustrierter Leitfaden zur TNM/pTNM-Klassifikation maligner Tumoren. 5th ed. Berlin: Springer; 2004. ISBN-10: 3540000429, ISBN-13: 978–3540000426

The following steps are performed: An esophagoscope is introduced to identify the openings of the diverticulum and the esophagus. The bivaled diverticulum scope is inserted, the longer blade is placed in the esophagus, the shorter blade in the diverticulum. The blades are opened to expose the mucosal septum. The esophageal mucosa is protected with moistened swabs. The mucosal septum is then resected with CO_2 laser in the midline in superpulse mode with low energy, and during resection, the different layers are appreciated (mucosa, fibers of cricopharyngeus muscle). The incision is approximately 5 mm before the fundus of the diverticulum. Postoperatively, the following measures are advisable to rule out complications (hemorrhage, perforation with emphysema, or mediastinitis): protective antibiotic coverage, 5 days of nasogastric tube feeding, a chest X-ray after 24 h, and a swallowing study 6 weeks postoperatively.

Microscopic CO2 laser excision is the gold standard for malignant lesions of the larynx and hypopharynx offering a focused laser beam and cuts without almost no carbonization. It offers safe removal with excellent functional outcomes.

Conclusion

Indirect laryngoscopy performed with rigid or flexible instruments under topical anesthesia offers a “bird’s eye” view combined with a possible evaluation of function – this is not possible under general anesthesia. Areas in which “hidden” primary tumors may occur should be carefully evaluated: base of tongue, wall of vallecula, piriform sinuses, base of epiglottis, and ventricular and subglottic space. While the

patient is under general anesthesia, palpation of the tongue base, floor of the mouth, lateral oropharyngeal walls and lower portion of the nasopharynx is mandatory. Bimanual examination with the finger inside and the opposite hand on the area of the neck should also be done.

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Assessment of Vocal Cord Function and Voice Disorders

14

Phillip Song

Introduction

The comprehensive voice assessment is a multidisciplinary examination that includes several different components: a voice-specific history, clinical laryngeal examination with rigid and/or flexible laryngoscopy, videostroboscopy, perceptual voice analysis, acoustic recordings, objective acoustic and aerodynamic data, and physical examination. There are different members of a voice team including laryngologists, speech and language pathologists, respiratory therapists, pulmonologists, allergists, and vocal pedagogues. The purpose of this chapter is to introduce the fundamental components of the laryngeal examination including laryngoscopy and stroboscopy as well as discuss common voice disorders. Focus will be on the instrumentation, technique, and discussion of pathology that may be pertinent for the airway and interventional pulmonology.

Voice is the product of a complex interplay between the chest, larynx, pharynx, and oral cavity. Our understanding of laryngeal physiology, especially as it pertains to voice production, has evolved from different disciplines including musicology, phonology, endoscopy, and head and neck surgery. Instruments for performing tracheostomy and endoscopy have been found among ancient artifacts of Pompeii and Egypt. The current instruments for the office examination of indirect laryngoscopy using an angled curved mirror and outside light source were developed by Dr. Philip Bozzini in 1807. And in the 1825 and 1827, there were European reports of evaluating the larynx using this method. The first individual to describe voice production as a component of laryngeal function was a baritone opera singer and music professor named Manuel Garcia. Using an angulated dental mirror, he was able to visualize his vocal folds during complex phonatory maneuvers. He observed that the vocal folds closed together to produce sound and opened during respiration. He noted that the tension and length of the vocal folds increased with pitch. He detailed his observations in a manuscript entitled "Physiological Observations on the Human Voice" and presented the paper before the Royal Society of London on May 24, 1855. In 1895, Alfred Kirstein modified a rigid esophagoscope to visualize the vocal folds that eventually gave rise to a generation of laryngoscopes. The laryngoscope enabled direct instrumentation of the larynx, enabling surgeons the ability to remove tumors, treat infectious disease, and remove foreign bodies. The introduction of the fiber-optic technology in the 1960s and 1970s gave rise to flexible nasopharyngoscopes and laryngoscopes which allowed for visualization of the larynx in a natural phonatory position. In the mid-1990s, dedicated laryngology fellowships became more widespread, producing another generation of surgeons into the evolving fields of laryngology, professional voice, and neurolaryngology.

The Voice History

Referral for a laryngeal examination for dysphonia is determined by risk factors, clinical behavior, and vocal demands of the patient. In general, the vast majority of hoarseness in the presence of other infectious symptoms referable to the throat spontaneously resolves. The American Academy of Otolaryngology in a clinical practice guideline recommended evaluation of the larynx for hoarseness of greater than 12 weeks duration regardless of risk assessment and clinical history. However, if there is a risk of malignant or progressive pathology, or if an individual is functionally impaired, assessment should come sooner. Hoarseness of unclear etiology in a high-risk patient with significant smoking and alcohol history requires expedient evaluation of the voice box. Vocal complaints by elite vocal professionals such as actors and singers may require immediate management and evaluation at the onset of symptoms.

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Table 14.1 Special topics to include within a voice history

Upper respiratory infections
Endotracheal intubations
Time coarse
Trauma
Profession and vocal demands
Vocal abuse
Tobacco, alcohol, and drug use
Dietary habits
Heartburn and acid reflux
Hydration
Allergy
Environmental and chemical exposures and reactions
Climate and seasonal changes
Heating and cooling units

The larynx has three primary functions, the regulation of the deglutination, respiration, and phonation. The voice history is focused on the nature of the laryngeal dysfunction: difficulty swallowing, difficulty with phonation, and respiratory difficulties, and these three functions should be seen as the larynx-specific review of systems. Regardless of the nature of the voice complaint, associated symptoms such as dysphagia, odynophagia, respiratory difficulties, loud breathing, dyspnea on exertion, coughing or choking during meals, or frank aspiration should be elicited. Reflux-related symptoms are also frequently encountered during the voice history, and symptoms such as globus, heartburn, altered taste, and excessive mucus/phlegm should be recorded (Table 14.1).

When describing voice complaints, it is important to note that definitions of hoarseness can vary considerably. The patient's self-perception of the vocal complaints may not be proportionate to the perception by an observer. Oftentimes emotional factors or social factors, such as the diagnosis of throat cancer in a family member, can bring specific awareness for one's own voice problem that might otherwise have been neglected. Causes of hoarseness prompting investigation are often inaccurate. Laryngitis is considered a common and normal experience and attributed to a myriad of things such as colds and other infections (tonsillitis, strep throat, pneumonia, bronchitis, etc.), allergies, overuse, environment, and reflux.

Hoarseness is a general term that refers to a variety of voice problems. There is no physiological or perceptual definition for hoarseness, and the examiner should try to direct and focus the patient toward more specific symptoms and problems. Examples include change in the quality of voice, altered pitch, changes in vocal stamina, strain, early vocal fatigue, loss of range, inability to project, inability to be heard, difficulty with articulation, or alteration in clarity. In addition, other components of the voice history should include details regarding the onset of symptoms (gradual or sudden), environmental issues (seasonality, pets, chemical triggers, and sensitivities), precipitating events (upper respiratory infections, stress, travel, screaming or shouting), and exacerbating factors (telephone use, diet, and reflux).

Onset of voice problems and inciting factors should be elicited and recorded. An acute onset of voice loss suggests a sudden change in vocal fold pliability or altered vocal behavior. Sudden voice changes occur with vocal hemorrhage, infectious laryngitis, vocal polyp, vocal fold paralysis, and muscle tension dysphonia. More gradual onset of voice changes suggests a more insidious or slow-growing process such as the development of vocal fold nodules, scarring, Reinke's space edema or polypoid corditis (smoker's larynx), presbylarynges, laryngopharyngeal reflux, vocal fold keratosis or leukoplakia, and laryngeal cancer. Most voicing disorders, especially in the early stages, will have fluctuating levels of dysphonia. For instances, patients with vocal fold nodules will have a preexisting history of recurrent "laryngitis" with return of normal voice. Vocal fold paralysis may result in a substantial loss of projection and vocal stamina; however, the degree of dysphonia may vary considerably based on the resting position of the immobile vocal fold, the degree of vocal fold edema, and overall energy level of the patient.

The quality of life impact of phonatory disorders is highly specific and individual to the patient. An examiner's perception may not correlate with the patient's perspective on the severity of the issue. The magnitude of the clinical problem may not correlate with the perceptual evaluation of hoarseness. The most important factor assessing the impact of someone's voice dysfunction is usually *occupation*. The social history is important. A hoarse librarian will not have the same level of impact from dysphonia as a professional singer. The impact of voice dysfunction tends to be highly varied from individual to individual. Some individuals are highly aware of small differences and changes in voice and alterations in voice timbre or frequency. Those with vocally demanding occupations tend to be more aware of minute voice changes than those who do not have significant voice use. Professionals who rely heavily on their voices, such as actors and singers, represent a special class of patients: elite vocal athletes. These individuals produce heavy demands on the vocal folds and test the limits of vocal abilities. Shear trauma or phonotrauma in these individuals are exceedingly high, making them susceptible to vocal injury.

Vocal users can generally be placed into three categories based on voice requirements: the standard user, the vocal professional, and the elite vocal performer. The elite vocal performer is required to use the extreme ranges of his or her phonatory abilities on a daily basis for income. This group includes professional actors, singers, and presenters.

Table 14.2 Voice handicap index (VHI)

Instructions: these are statements that many people have used to describe their voices and the effects of their voices on their lives							
Circle the response that indicates how frequently you have the same experience							
0 = Never 1 = Almost never 2 = Sometimes 3 = Almost always 4 = Always							
Part I: functional							
F1	My voice makes it difficult for people to hear me	0	1	2	3	4	
F2	People have difficulty understanding me in a noisy room	0	1	2	3	4	
F3	My family has difficulty hearing me when I call them throughout the house	0	1	2	3	4	
F4	I use the phone less often than I would like to	0	1	2	3	4	
F5	I tend to avoid groups of people because of my voice	0	1	2	3	4	
F6	I speak with friends, neighbors, or relatives less often because of my voice	0	1	2	3	4	
F7	People ask me to repeat myself when speaking face-to-face	0	1	2	3	4	
F8	My voice difficulties restrict personal and social life	0	1	2	3	4	
F9	I feel left out of conversations because of my voice	0	1	2	3	4	
F10	My voice problem cause me to lose income	0	1	2	3	4	
Part II: physical							
P1	I run out of air when I talk	0	1	2	3	4	
P2	The sound of my voice varies throughout the day	0	1	2	3	4	
P3	People ask, "What's wrong with your voice?"	0	1	2	3	4	
P4	My voice sounds creaky and dry	0	1	2	3	4	
P5	I feel as though I have to strain to produce voice	0	1	2	3	4	
P6	The clarity of my voice is unpredictable	0	1	2	3	4	
P7	I try to change my voice to sound different	0	1	2	3	4	
P8	I use a great deal of effort when I speak	0	1	2	3	4	
P9	My voice is worse in the evening	0	1	2	3	4	
P10	My voice "gives out" on me in the middle of the speaking	0	1	2	3	4	
Part III: emotional							
E1	I am tense when talking to others because of my voice	0	1	2	3	4	
E2	People seem irritated with my voice	0	1	2	3	4	
E3	I find other people don't understand my voice problem	0	1	2	3	4	
E4	My voice problem upsets me	0	1	2	3	4	
E5	I am less outgoing because of my voice problem	0	1	2	3	4	
E6	My voice makes me feel handicapped	0	1	2	3	4	
E7	I feel annoyed when people ask me to repeat	0	1	2	3	4	
E8	I feel embarrassed when people ask me to repeat	0	1	2	3	4	
E9	My voice makes me feel incompetent	0	1	2	3	4	
E10	I am ashamed of my voice problem	0	1	2	3	4	

Adapted from source: Jacobson B, Johns A, Crywalski C, Silbergleit A, Jacobson G, Benninger M. The voice handicap index (VHI): development and validation. Am J Speech Lang Path. 1997;6(3):86–70

Vocal professionals are required to speak in public with large groups on a regular basis; this category includes teachers, clergy, politicians, and attorneys. The standard user or non-vocal professional is not significantly impacted with mild hoarseness or vocal fatigue.

Because the impact of phonatory disorders is highly variable and may not correspond measurably to perceptual difference in actual voice, we frequently utilize quality of life scales. The Voice Handicap Index (VHI) and its abbreviated form, the VHI-10, the Voice Outcome Survey (VOS), and the Voice-Related Quality of Life Survey (VRQL) are all examples of such quality of life measurements (see Tables 14.2 and 14.3). It is extremely useful to have patients fill out these self-questionnaires at the initial visit as well as during subsequent follow-up especially if a medical or surgical intervention has taken place (Table 14.4) (Box 14.1).

Table 14.3 Voice handicap index – 10 (VHI-10)

F1	My voice makes it difficult for people to hear me	0	1	2	3	4
F2	People have difficulty understanding me in a noisy room	0	1	2	3	4
F8	My voice difficulties restrict personal and social life	0	1	2	3	4
F9	I feel left out of conversations because of my voice	0	1	2	3	4
F10	My voice problem cause me to lose income	0	1	2	3	4
P5	I feel as though I have to strain to produce voice	0	1	2	3	4
P6	The clarity of my voice is unpredictable	0	1	2	3	4
E4	My voice problem upsets me	0	1	2	3	4
E6	My voice makes me feel handicapped	0	1	2	3	4
P3	People ask, "What's wrong with your voice?"	0	1	2	3	4

Adapted from source: Rosen CA, Lee AS, Osborne J, Zullo T, Murry T. Development and validation of the voice handicap index-10. Laryngoscope. 2004;114(9):1549–1556

Table 14.4 Clinical characteristics of common vocal fold pathology

Pathology	Onset	Symptoms (general)
Vocal nodules	Gradual, preceded by recurrent and prolonged laryngitis	Frequent voice loss, roughness, and strain in the voice. Easy vocal fatigue and inconsistency
Vocal polyp	Sudden, subacute, generally worse acutely with mild improvement over time	Significant roughness and strain. Difficulty with projection and very inconsistent voice
Vocal hemorrhage	Sudden onset of voice loss with improvement almost back to baseline	In the beginning, severe roughness and strain, improving to mild to moderate roughness
Laryngeal granuloma or contact ulcer	Preceding history of intubation or gradual onset	Globus sensation, excessive throat clearing, roughness, and vocal strain
Laryngeal web	Preceding history of surgery or laryngeal trauma, gradual loss of voice	Gradual loss of voice and projection. One of the rare physiological causes of aphonia
Subglottic stenosis	Gradual	Progressive difficulty primarily with projecting the voice and stamina
Bilateral vocal fold immobility	Gradual or sudden	Voice is strained and rough, but not weak. Breathing symptoms predominate
Unilateral vocal fold immobility	Sudden, subacute	Breathy, weak, and asthenic voice. Easy vocal fatigue and pitch may increase. May complain of breathlessness
Laryngeal cancer	Gradual or subacute	Voice is typically rough and strained with decreased pitch

Box 14.1 Common Self-Assessment Measures of Voice

VHI
VHI-10
VOS
VRQL

Physical Examination of the Larynx

The physical examination should always include a complete examination of the head and neck and may also include relevant inspection of other systems including respiratory, gastrointestinal, and neurological based on history and clinical suspicion. The chapter's focus will be on the laryngeal examination in particular for the diagnosis of voice conditions.

The mucosal tract of the oral cavity, oropharynx, nasopharynx, larynx, and respiratory system all contribute to voice production. These areas should be inspected for mucosal lesions, masses, and movement abnormalities. Examination of the mucosal quality should be carefully performed. Normal, well-hydrated mucosa is important for good sound production, and the presence of abnormal mucosal surfaces, excessive dryness, thick phlegm/mucus, purulent drainage, and fungal changes will result in dysphonia. The tongue and palate should be inspected for good mobility. The nasal exam should include an evaluation for mucosal hypertrophy and allergic changes.

The neck examination should include manual palpation of the neck and thyroid. The larynx should be mobile and minimally tender. During swallowing, the larynx should elevate several centimeters freely and comfortably. However, during comfortable phonation, there should be relatively little vertical elevation of the larynx. The cricothyroid space and the thyrohyoid space should be palpated during phonation. Excessive tension or tenderness of these areas during phonation or during inspection would suggest excessive strain or the recruitment of supraglottic muscles to achieve voice. A highly strained and excessively effortful voice may reveal excessive elevation of the larynx, a very short and tender thyrohyoid and cricothyroid spaces, and tight pharyngeal and strap muscles.

Perceptual Voice Examination

Perceptual voice analysis is a physical examination component of the laryngeal exam. The examiner is hearing and analyzing the voice quality in order to correlate the findings on laryngoscopy. During the course of an exam, the patient may sound stressed or anxious, there may be difficulty with projection, or a high degree of strain may be present. The voice may sound flat and disaffected or too emotional. On many levels, all clinicians respond to these differences but often do not act or document these observations. Perceptual voice analysis is a skill which can be augmented by practice and observing voice differences and abnormalities in a systematic and conscious manner.

There are several perceptual voice scales that are in common usage in the voice and speech-language field. Common voice scales include the GRBAS scale and CAPE-V. The GRBAS scale was developed in the 1970s by the Japanese Phoniatric Society. It is widely used and internationally adopted in a wide variety of languages. The GRBAS scale is

a perceptual rating scale with five basic parameters. The scale *Grade(G)* stands for the assessment of the global degree of dysphonia. *Roughness(R)* is the perceived quality of irregular vibration from the larynx and corresponds to irregular fluctuations of the fundamental frequency or amplitude of the glottal sound source. *Breathiness(B)* is the voice quality produced by turbulence, air leak, and/or glottal incompetence. *Asthenia(A)* is weakness of spontaneous phonation. And *Strain(S)* or vocal hyperfunction is the auditory impression of excessive effort and tension.

Another common perceptual analysis tool is the CAPE-V, a rating scale using parameters of severity, roughness, breathiness, strain, pitch, and loudness, using a 10-cm visual analog scale on a standardized reading passage (see Box 14.2). The voice evaluation is not limited to these scales but is a part of a comprehensive description of the voice and its dysfunction. Oftentimes, patients will be asked to focus in and concentrate on a component of their symptoms to better elucidate the problem while the examiner assists in applying relevant descriptors and terminology. The goal of the symptom assessment is to take a global descriptor like hoarseness and to break it down into separate components of dysphonia in order to be able to identify individual aspects of laryngeal dysfunction.

Box 14.2 (CAPE-V)

CAPE-V
GRBAS

Vocal Fold Anatomy and Physiology

Voice is the product of many different structures including lungs, chest wall, neck, pharynx, larynx, oral cavity, nasal cavity, and face. The lungs provide the air and the power to the vocal tract. The vocal folds close to generate subglottal air pressure which is released through the laryngeal valve in the form of a stream of controlled air "puffs" which produce acoustic wave vibration. The vocal folds are known as the "sound generator." The pharynx, oral cavity, and lips manipulate the acoustic vibration to provide resonance and articulation. The neurophysiological control of the larynx is complex and poorly understood. One of the hallmarks of the voice exam is that form does not always follow function, meaning that two identical pathological findings on the vocal folds may produce substantially different types of vocal dysfunction. Because of the complexity of the vocal system and the ability of individuals to compensate for a severely disordered larynx, treatment should be tailored to the patient, not the pathology.

The vocal fold is a trilaminar structure. Composed of epithelium, lamina propria, and muscle, the true vocal fold is physiologically adapted to produce vocal fold vibration. It has an innate viscoelastic property which allows it to produce vibratory pitch within physiologic limits of subglottal airflow. The medial edge is adapted to sustain repetitive trauma produced by these vibrations. Most of what we know about vocal fold vibration and the function of the vocal cord is attributed to the work of Minoru Hirano in the 1970s. It was his observations that led to the development of the current theory of voice production and vocal fold vibration which is the cover-body theory. The basis of this theory is that there are two distinct structural elements to the vocal folds, the *cover* which is composed of epithelium and vibratory tissue (superficial lamina propria) and the *body* which is the more rigid underlying elements (muscle, ligament, deep lamina propria). Examination of the vocal folds evaluates the *cover* predominantly. The musculomembranous vocal fold refers to the medial edges of the vocal folds which extend from the vocalis process of the arytenoid cartilage to the anterior commissure. The striking zone is an area where the vibration of the vocal folds is felt to be at maximum amplitude and is present at the junction between the anterior and middle third of the musculomembranous vocal fold. A variety of phonotraumatic lesions such as nodules, polyps, and cysts occur in this region. The arytenoid complexes are composed of the arytenoid cartilages and the two sesamoid cartilages, the corniculate and cuneiform, which are suspended above the arytenoid. The cricoarytenoid joint is a synovial joint which has rotational as well as translational motion. The arytenoid cartilage has two processes, the medially oriented vocalis process which points toward the airway and provides the attachment to the vocalis muscle (the medial belly of the thyroarytenoid muscle) and vocal folds and the lateral muscular process.

The vocal folds function to produce acoustic signal by transforming mechanical energy of vocal fold vibration into acoustic energy with aerodynamic vibration. An ideal vibration can be produced by smooth mucosal edges that close easily by two vocal folds with symmetrical rheological properties and elasticity. This produces an efficient translation of aerodynamic pressure into acoustic signal.

All methods of physical examination of the vocal cords are from the superior viewpoint. Whether with a rigid or flexible endoscope or with indirect laryngoscopy, views are always from the top looking inferiorly to the base of tongue, epiglottis, superior aspects of the arytenoids, piriform sinuses, true vocal folds, and supraglottis. Areas which are difficult to view from the superior position are the laryngeal ventricles, sandwiched between the true and false vocal folds, the infraglottic segment, the posterior vocal cords, which are sometimes obscured by the arytenoid complex, the pyriform sinuses which are often hidden within folds of

tissue, and the vallecula which can be obscured by lymphoid hypertrophy. The postcricoid area of the cervical esophagus is a difficult area to view because the area is usually held closed by the action of the cricopharyngeus muscle. In addition, when the larynx is compromised, the natural adaptive behavior is to contract the false vocal folds and supraglottis, which often obscures visualization of the true vocal cords.

Office-Based Examination of the Larynx

Indirect Laryngoscopy

Office-based assessment of the larynx is performed in several different ways. The most common method is *indirect laryngoscopy* using an angulated dental mirror and headlamp. The angulated mirror when inserted correctly into the oropharynx with a directed light source can be used to visualize the true vocal fold, false vocal folds, arytenoids, and supraglottic structures quite adequately. The exam is limited by the patient's anatomy and ability to tolerate an instrument deep within the back of the throat. A substantial gag reflex, a large palate, enlarged base of tongue, cervical osteophytes, and hypertrophic tonsils can prevent examination.

Flexible Transnasal Laryngoscopy

The 1960s and 1970s gave rise to fiber-optic technology and the development of small-diameter fiber-optic endoscopes. Inserted transnasally, these fiber-optic endoscopes could visualize the larynx as the patient performs normal laryngeal tasks. The advent of digital imaging technology has given rise to a new generation of flexible laryngeal scopes or nasopharyngoscopes which has improved the visualization further. High-definition imaging with the use of a special light filters have also improved the diagnostic sensitivity of the examiner. To perform transnasal laryngoscopy or nasopharyngoscopy, the nasal cavity is topically anesthetized with lidocaine and a nasal decongestant. The endoscope is inserted into the nose toward the nasopharynx. Generally, entrance along the floor of the nasal cavity is preferred, as the sensory innervation is denser in the more superior segments. The endoscope is guided into the oropharynx until the vocal folds are in view.

Once the epiglottis and vocal folds are visualized, the patient is instructed to produce a steady/i/at a comfortable pitch and volume and again at a high and low register. The flexible endoscope also allows for visualization of the larynx during complex phonatory tasks, such as speaking and singing, and vegetative tasks (coughing, laughing, and throat clearing). Implementing a standardized reading passage and a singing sample (for singers) is an important component of the flexible examinations.

Rigid Telescope

The angulated rigid telescope is also an excellent method for visualizing the true vocal folds. The degree of angulation is generally 60°, 70°, or 90°. The rigid telescope allows for excellent visualization of the true vocal folds with substantial light and magnification. The rigid telescope is often paired with a stroboscopy unit which is used to determine the pliability or mucosal ways of the vocal folds.

Videostroboscopy

Videostroboscopy is a powerful tool designed to evaluate the pliability of the vocal fold and the larynx's ability to generate the mucosal wave. The vocal fold is a multilayered structure with several different components responsible for phonatory vibration, and the mucosal wave forms the basis for vocal fold vibration and the generation of an acoustic signal. The stroboscopy unit is essentially a flashing light that is calibrated to the frequency of phonation. The flashing light, or strobe, renders an optical image that seemingly slows down the vibratory movement or "mucosal wave" of the vocal folds. The stroboscopy unit is usually paired with a video system to record and document the examination, and the pairing is referred to as videostroboscopy. Because the viscoelastic properties of the vocal folds determine the signal characteristics of voice production, videostroboscopy is an important component of the examination of dysphonia. The magnified view of the medial edge of the vocal folds allows for diagnosis of mass lesions, scar, adynamic components, and loss of tissue. In addition, the depth of a mucosal or submucosal lesion can be better understood by evaluating the impact of the mass on the mucosal wave. A superficial keratosis or leukoplakia will appear to float along the surface of the vocal fold while an invasive carcinoma will stick down to the deeper laryngeal structures.

The instrumentation needed to perform videostroboscopy includes a stroboscopic unit which generates the light and a microphone which captures the frequency of the acoustic signal. An electroglottograph, a device that can measure electrical resistance across the vocal folds using surface electrodes, can also capture the frequency of vocal fold closure to aid the stroboscopic unit. A video capture system that includes a monitor, a rigid or flexible endoscope, and camera is also necessary. Recording and archiving the examination is important because stroboscopic interpretation often requires several repeated rounds of viewing.

Videostroboscopy can be performed with a flexible endoscope or rigid telescope. Stroboscopy is typically performed with a 90° or 70° rigid telescope. The rigid telescope allows for a bright, magnified, and high-quality image. The image quality obtained with the rigid telescope cannot be matched with a traditional flexible fiber-optic laryngopharyngoscope; however, the newer distal chip flexible laryngoscopes are coming close.

The performance of rigid videostroboscopy can vary among practitioners. The basic procedure begins by placing the patient in a "sniffing" position. The patient sits forward, with hands or elbows resting lightly on the knees, along with the neck and chin extended. The mouth is opened, and the patient extends the tongue forward out of the mouth. The patient or practitioner can grasp the tongue in the forward position with a cotton pad or 4 × 4 gauze. The rigid telescope is inserted along the floor of the mouth until the larynx or the epiglottis is visualized. Patients with highly sensitive gag reflexes may have difficulty tolerating this portion of the examination. Care should be taken to avoid striking the anterior tonsillar pillars and the posterior pharyngeal wall, as these areas are particularly sensitive. Patients with significant difficulty may benefit from application of a topical anesthetic such as cetacaine or lidocaine.

Once the epiglottis or vocal folds are visualized, the patient is instructed to produce a steady/i/at their most comfortable pitch and volume. This is the fundamental frequency. The majority of the interpretation should be carried out at this frequency. The patient is then instructed to produce a steady/i/at their upper pitch range and then again at their lowest register. Increasing the pitch will lengthen and tense the vocal folds, thereby highlighting adynamic segments, and bringing submucosal lesions more superficial and easier to delineate. The lower pitches can also highlight adynamic segments, especially sulcus deformities. Additional maneuvers to perform during the evaluation include a pitch glide or glissando, where the patient goes from the lower register to the upper in a continuous stream. Brisk nasal inhalation "sniffs" or alternating "sniffs" with/i/can reveal the range of abduction of the vocal folds.

Stroboscopy is a method of assessment rather than an objective test. There are several obstacles in the interpretation of videostroboscopy, the most fundamental of which is the lack of a standardized and reliable methodology of evaluation. There have been several attempts to make a uniform grading system for stroboscopic evaluation; however, no single methodology has been universally accepted. There is inherent variability in the interpretation of the examination that has been well illustrated within the literature. Inter- and intrarater reliability has been an issue ranging from correlation values of 0.20–0.85.

Interpretation of the Laryngeal Exam

There are different components of the examination that should be noted during interpretation. They can be basically broken down into three categories: anatomy, laryngeal motion, and mucosal wave properties. For the sake of consistency, a standardized form should be used so that all components of the examination can be commented.

Anatomic components include an assessment of supraglottic and laryngeal structures, especially when describing lesions along the medial vocal fold length. Mucosal lesions, trauma, inflammation, and masses along with description of distribution, location, and size should be noted.

Laryngeal motion includes a functional assessment of gross vocal fold motion, symmetry and supraglottic function. Special care should be taken to note supraglottic hyperfunction and glottic closure pattern. Hirano and Bless described several different glottic closure patterns. These include complete, incomplete, hourglass, irregular, posterior gap, anterior gap, and spindle gap. Authors have described adding a variable pattern to describe those conditions where a consistent closure pattern is not seen. Supraglottic compression may be altered between flexible and rigid stroboscopy. In particular, the forced anterior extension of the tongue will alter the hyperfunctional state of the larynx. A description of the supraglottic compression should be included. A common classification system for supraglottic compression divides the types into an open posterior gap-type hyperfunction, predominantly lateral overclosure, predominantly anterior-posterior overclosure, and sphincteric closure.Mucosal wave properties are an assessment of the pliability of the vocal folds and the larynx's ability to generate vibratory energy taken during videostroboscopy. Mucosal wave properties include phase closure, amplitude and phase symmetry, periodicity, adynamic or nonvibratory segments, and duration of closure. Mucosal wave characteristics should be recorded at the patient's comfortable or habitual pitch which reflects the fundamental frequency.

Periodicity describes the cycle to cycle regularity of successive acoustic waves. A periodic signal implies a clear, resonant pitch without significant variations between vibratory cycles. An aperiodic or irregular signal implies significant differences in vibratory cycles, producing a rough or multitextured acoustic signal.

Duration of closure or the closed phase of the mucosal wave is the length of time, relative to the vibratory cycle, that the vocal folds remain in a closed position. The duration of closure can be determined based on a gestalt or approximate measure or more quantitatively by measuring the length of the closed phase with digital photography or videokysmography.

Mucosal wave amplitude describes the horizontal excursion of the vocal folds and is an indication of the viscoelastic properties of the vocal fold. It is a somewhat subjective description, as the amplitude can vary depending on pitch, frequency, effort and volume. Other factors such as angulation of the endoscope and supraglottic compression can influence the degree of vocal fold show.

The authors encourage the use of templates and procedure notes to maintain consistency for stroboscopic interpretation. There are numerous rating scales that have potentially good applications; however, none have been demonstrated to be uniquely superior. The universal adoption of a common template form and method for assessment should be a goal for the future as well as improved methodology to increase inter- and intrarater reliability. Review of examinations performed in the past is also encouraged so that internal reliability for the individual practitioner can be established. Consistency has not been demonstrated and by no means should it be taken for granted even among experienced evaluators. An intrarater reliability of 0.80 or greater is desirable. Dissemination of a standardized and rigorously tested template would be a valuable resource and a useful tool for testing interpreter reliability and consistency.

Voice Analysis Equipment

Voice quality assessment is based on a subjective impression of vocal quality and varies between different observers based on experience. Objective voice analysis measures have been the focus of research and study. Acoustical analysis and airflow studies are an instrumental measure of voice and a useful adjunct for vocal analysis. Notably, these measures can help localize areas of dysfunction within the phonatory mechanism and are quantifiable values that can be used to measure progress of therapy.

There are numerous tools available to the laryngologist that will assist in the localization of dysfunction. Much effort has been expended in acoustic and speech study toward the search for standardized acoustic parameters that are reliable and reproducible among different subjects and have diagnostic value for various vocal pathologies. Although no perfect acoustic analysis measure has yet to be identified, these measures are useful for following effectiveness of therapies. By building a body of normative data, these parameters may have further applications in the future.

The most basic and fundamental instrumental voice analysis tool is audio recording. Digital audio recording of a standardized passage such as the Rainbow passage (*see* Box 14.3) is useful as a baseline assessment.

The *frequency* is the rate of vibration of the vocal folds measured in cycles per second or Hertz. The *fundamental frequency* is the natural or most comfortable pitch delivered by the larynx in a given individual. The pitch of the voice and fundamental frequency are inversely related. Pitch can be measured by wave form analysis of the voice. Smooth vocalizations when digitized form periodic waves that can be graphically represented. The mean fundamental frequency is an average value that is calculated during sustained vowels or extracted during speech. The *phonation range* is the range of fundamental frequencies an individual can produce, which is an important characteristic for singers.

Intensity is a measure of loudness. On an acoustic waveform, intensity corresponds to the amplitude height. Maximal and minimal intensity can be measured at different fundamental frequencies to graph a phonetogram. Like an audiogram, the phonetogram is a visual representation of the vocal range in a given individual. Care must be taken when evaluating phonetograms as both frequency range and intensity range are effort dependent and can vary when changing testing environments. Standardization is extremely important when eliciting these values.

Jitter and shimmer are two perturbation measures. Perturbation is the cycle to cycle variability of the acoustic waveform during a sustained vowel. Shimmer is the perturbation in intensity or loudness, and jitter is the perturbation in frequency. These measures correspond to how smooth a voice sounds. These values are most consistent in the *absence* of significant dysphonia/dysarthria as it takes a sustained uninterrupted vowel sound to measure wave forms. Perturbation parameters are not useful for patients with severe dysphonia and dysarthria; however, they can be used to evaluate clinical treatment efficacy.

Signal to noise ratios are measures comparing harmonic signal energy to aperiodic or noise energy. During smooth, uninterrupted vocalization, the majority of energy is harmonic and forms well-defined, periodic waveforms. As the mucosal wave is disrupted, the acoustic waveforms become irregular, forming white noise. Generally, large noise energy with greater random aperiodicity represents abnormal vocal function.

Acoustic analysis testing in general requires a rigorously standardized testing environment, skilled evaluators, and highly motivated voice users. Accurate wave forms are difficult to elicit in the presence of severe dysphonia or dysarthria, rendering most parameters inconsistent. While clinical correlation to mucosal wave vibration, glottic closure and power is possible, acoustic parameters do not have diagnostic value for the localization of vocal pathology.

Box 14.3 Rainbow Passage

When the sunlight strikes raindrops in the air, they act like a prism and form a rainbow. The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow.

Source: Fairbanks G. Voice and articulation handbook. 1960:127. Copyright 1960 by HarperCollins Publishes Inc.

Aerodynamic Measurements

Because of the important role of the lungs in vocal production, pulmonary function testing is helpful for the evaluation of weak and asthenic voice and vocal fatigue. The lungs provide ventilatory support needed to initiate the mucosal wave.

Subglottal pressure can be measured directly through the introduction of a pressure transducer through the trachea; however, most of the subglottic pressure measurements are made indirectly. By holding the transducer in the mouth, pursing the lips tightly and exhaling, an indirect measure of subglottal pressure via transoral pressure is obtained. Normative testing has shown that the minimal subglottic air pressure needed to support voice is between 3 and 7 cm of water. Average airflow rates between the vocal cords are around 50–200 ml of water. Phonation threshold is the minimal subglottal pressure needed to initiate vocal fold vibration. Taken together, these aerodynamic measurements provide a sample of laryngeal valve function and mucosal wave integrity.

In general, objective measurements of acoustic and aerodynamic voice analysis suffer from similar problems when using them clinically. Instrumental standardization has not yet been fully implemented so that readings taken with different equipment and in different laboratories are not necessarily comparable. A high degree of technical expertise is required both to administer these tests and to interpret the results. The type of speech sample used also affects results. These tests require a high level of understanding and function for the subject and a number of these tests are effort dependent. For severely dysphonic patients, there is considerable variability in testing results.

Common Vocal Problems

Common voice problems related to laryngeal pathology can be broken down into several different categories, nonorganic or functional voice disorders, motion or movement disorders, and anatomic laryngeal pathology which disrupts the mucosal wave. There is a great deal of controversy in the laryngology literature regarding definitions of common vocal fold pathology. This chapter will try to maintain consistency with descriptions and labels, although in practice there may be significant differences between definitions from one interpreter to another. Although a comprehensive discussion of causes of dysphonia is beyond the scope of this chapter, an attempt will be made to describe the most commonly encountered etiologies in the voice clinic.

Functional Voice Disorders

Functional voice disorders are nonorganic vocal problems that are characterized by dysphonia secondary to inappropriate alteration in vocal tension without anatomic, physiological, or neurological basis. Laryngeal anatomy is normal or near normal, and the symptoms are disproportionate to the examination findings. The motion of the vocal folds is intact and symmetric, and there is no discernable laryngeal pathology that corresponds to the hoarseness. Hoarseness, and the perceived level of dysphonia, is often much more severe than the laryngeal findings. The symptoms can be highly variable. The voice can be strained or breathy, weak or excessively loud, and consistent or inconsistent. There can be pitch alterations. During the laryngeal exam, attention is carefully made at the behavior of the larynx. There are often features of excessive force or traction on the vocal folds, with increased contraction and function of the supraglottic larynx and extralaryngeal tension. Clinically, the patient has a highly strained vocal quality as well as features of excessive work of voicing. The neck is often tight and tender to palpation, especially in the thyrohyoid space and cricothyroid space, and the larynx is in a high, tight position against the hyoid bone.

The hallmark of functional voice disorders is disproportionate hoarseness relative to the laryngeal findings. The most common functional voice disorder is primary muscle tension dysphonia (MTD) or vocal hyperfunction. There is excessive tension and effort placed onto the vocal track producing a strained, strangled voice quality. Critical evaluation of which laryngeal muscles are dysfunctional is very important. Muscle tension dysphonia can be primary or secondary. Primary muscle tension dysphonia is often associated with

anxiety or laryngeal irritability. Secondary muscle tension disorder refers to hyperfunctional compensation secondary to some glottic abnormality or mucosal wave pathology. Secondary muscle tension dysphonia may be a very normal compensatory response.

There are several ways to categorize types of muscle tension dysphonia. Supraglottic manifestations of hyperfunction include *ventricular hyperfunction* which is overclosure of the false vocal folds over the true vocal folds, *anterior-posterior compression* which refers to overclosure secondary to the epiglottis and arytenoid complex narrowing, and *sphincteric closure* where both dimensions are incorporated, closing off the larynx. Muscle tension may also be the product of excessive tension of the vocal folds without significant supraglottic activity. There may be over rotation of the lateral cricoarytenoid muscle creating a posterior glottic gap and excessive vocalis process show, excessive cricothyroid muscle motion with a lengthened and tight vocal fold, or hyperfunction of the transverse arytenoid muscles causing a scissoring action of the posterior glottis. Voice therapy is the treatment of choice for vocal hyperfunction.

Motion Disorders of the Larynx

Motion disorders of the larynx are a group of disorders which manifests as abnormality of movement, impairing laryngeal function secondary to alteration in neurological input. The motion may be hyperkinetic or hypokinetic. Examples of hyperkinetic motion abnormalities include neurological diseases such as spasmodic dysphonia, laryngeal tics, myoclonus, and vocal tremor. Hypokinetic motions disorders include vocal fold immobility, paresis, or paralysis. These problems may require systemic medications, botulinum toxin injections to the larynx, voice therapy, and phonosurgery.

Vocal fold *immobility* is the descriptive term applied when there is a fixed vocal fold or if there is reduced motion observed during examination. Vocal fold paralysis and paresis is the result of neurological injury which affects the recurrent laryngeal nerve function. The major causes of vocal fold paralysis include iatrogenic injury (intubation, head and neck or cardiac surgery, trauma), neoplasm (lung, head and neck, and brain), and idiopathic. Vocal fold immobility may also be result of injury at the cricoarytenoid joint. Subluxation or dislocation of the joint can be the consequence of intralaryngeal trauma and intubation. There may also be mass effect from an adjacent neoplasm which interferes with the range of motion of the vocal folds.

Unilateral vocal fold immobility is typically a problem of glottic insufficiency. The voice is weak, breathy. There is early vocal fatigue, an inability to project, and excessive strain. There may be a feeling of running out of breath during speech or exercise

Bilateral vocal fold immobility may be the result of bilateral nerve injury but is more commonly a result of mechanical fixation. The mechanical fixation can be from bilateral cricoarytenoid joint fixation or posterior glottic scarring. The common causes of bilateral vocal fold fixation include prolonged intubation, intralaryngeal trauma, and radiation fibrosis. Laryngopharyngeal reflux has also been implicated in the development of posterior glottic scarring, and autoimmune diseases such as Wegener's disease can also produce glottic fixation. Bilateral paralysis (neurogenic) can be the result of tumors, strokes, and surgery, notably esophagectomy, total thyroidectomy, and tracheal resection.

Bilateral vocal fold immobility results in primarily respiratory symptoms, shortness of breath, difficulty breathing at night, exertional dyspnea, and biphasic stridor, while voice changes are usually minimal. In fact, in those operated on to open the airway, the return of voice is typically followed by return of breathing symptoms with restricted airflow.

Mucosal Wave Pathology

Vocal fold pathology which results in voice problems are generally those that disrupt normal vocal fold pliability and affect the mucosal wave. The mucosal wave refers to the vibratory wave of the vocal folds which produces the main sound signal. The viscoelastic properties of the vocal folds may be reduced or impaired by a variety of benign and malignant pathologies. In general, most of the anatomic lesions effecting voice in the larynx can be grouped as either *phonotraumatic* lesions which are a consequence of vocal overuse or *nonphonotraumatic* lesions.

Phonotraumatic lesions generally begin in the basement layer or subepithelial layer of the vocal folds and below and cause loss of the superficial lamina propria early in the presentation. This results in stiffness of the vocal fold and difficulty producing the mucosal wave. Common lesions which are phonotraumatic include vocal nodules (singer's or screamer's nodules), polyps, sulcus deformities, vocal hemorrhages, varices/ectasias, and cysts. Most nonphonotraumatic lesions arise from reactive epithelial-based lesions affecting the superficial surface. Epithelial changes include laryngeal squamous cell carcinoma and premalignant changes (leukoplakia and erythroplakia) and infections (recurrent respiratory papillomatosis, fungal infection, and bacterial and viral laryngitis). Certain conditions such as mucosal trauma, vocal fold ulcerations,

and anterior glottic webbing (see Fig. 14.1) are also epithelial based.

Common vocal fold pathologies which are phonotraumatic in origin include vocal nodules, polyps, and cysts. The etiology of these lesions is from excessive *phonotrauma*, the trauma created as the vocal folds strike each other during vibration. These lesions occur in a specific location of the vocal folds, the "striking zone," which is in the junction of the anterior and middle third of the musculomembranous vocal fold. These benign disorders have a characteristic appearance. Vocal fold nodules are typically symmetric with a broad base and significant scarring (see Fig. 14.2). Vocal fold polyps are typically unilateral raised mass lesions, although a small scar is commonly seen on the contralateral vocal fold (see Fig. 14.3). Both nodules and polyps are histologically similar and occur in the subepithelial layer or the basement membrane of the epithelium. Vocal cysts are deeper lesions and may be true epithelial-lined cysts or false cysts. The cysts can be tethered to the vocalis process, and the margins can extend a considerable distance beyond the actual mass lesion.

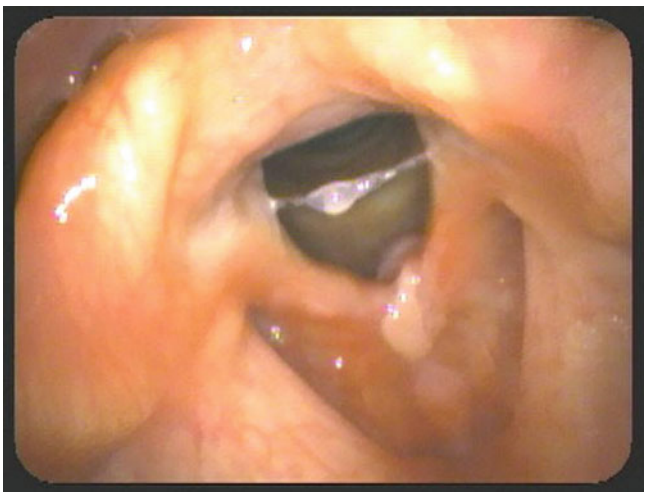

Fig. 14.1 Vocal fold cross-sectional histology (Reprinted from Hirano M. Clinical Examination of Voice in Disorders of Human Communication Vol. 5, Springer Verlag; 1981, with kind permission of Springer Science + Business Media)

Vocal ectasias and varices are abnormal distended blood vessels on the superficial surface of the vocal folds. The lesions can rupture with excessive pressure and lead to vocal hemorrhage (see Fig. 14.4).

Vocal fold pathologies which affect the epithelium include squamous cell carcinoma, leukoplakia, and keratosis. Squamous cell carcinoma is by far the most common malignancy of the vocal folds. Leukoplakia is a white patch on the vocal fold and implies a premalignant clonal proliferation of abnormal tissue. Keratosis or hyperkeratosis is the development of the white patch from excessive keratin formation on the normally nonkeratinizing epithelium of the vocal folds (see Fig. 14.5). Rates of progression from cellular atypia to squamous cell carcinoma vary from 5 % to 18 % depending on the degree of atypia. The impact on voice depends on the location of the lesion. Lesions anterior to and at striking zone will have earlier voice changes than those that occur elsewhere. Lesions in the laryngeal ventricles, false vocal folds, posterior true vocal folds, and arytenoids regions will need to be much larger and more exophytic to cause voice changes.

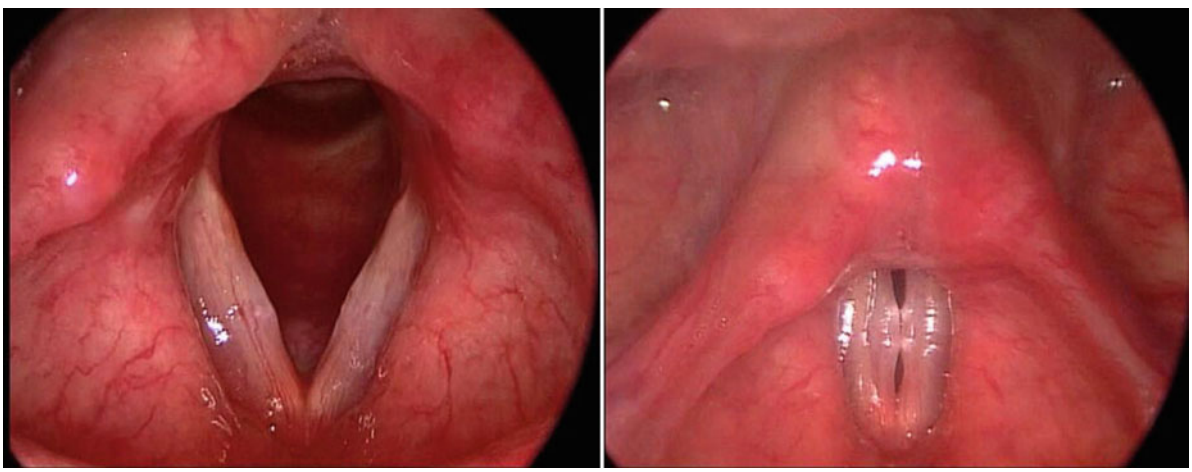

Fig. 14.2 Vocal fold anatomy

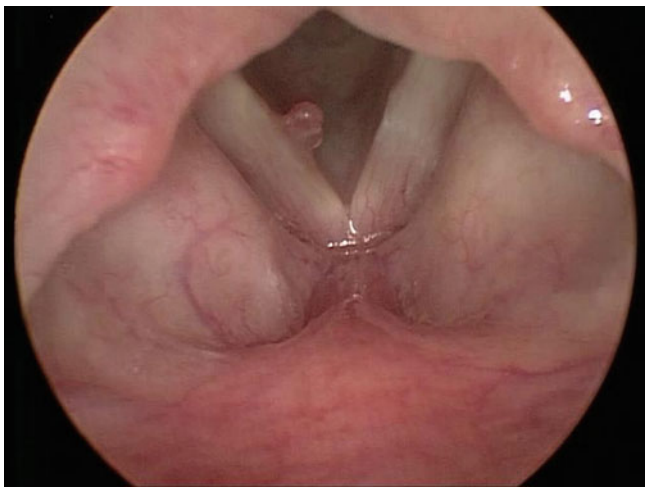

Fig. 14.3 View of indirect laryngoscopy

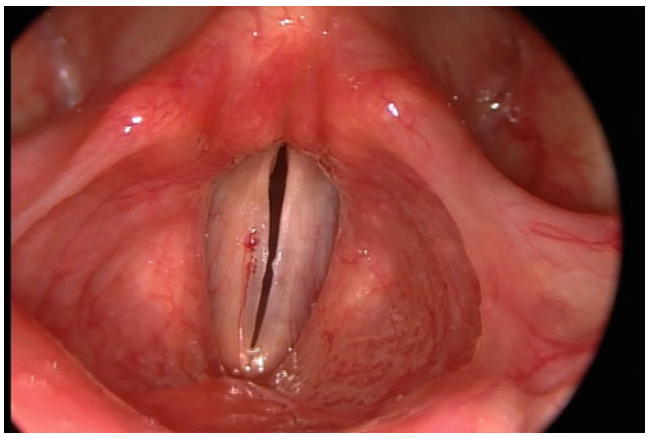

Fig. 14.4 Varix

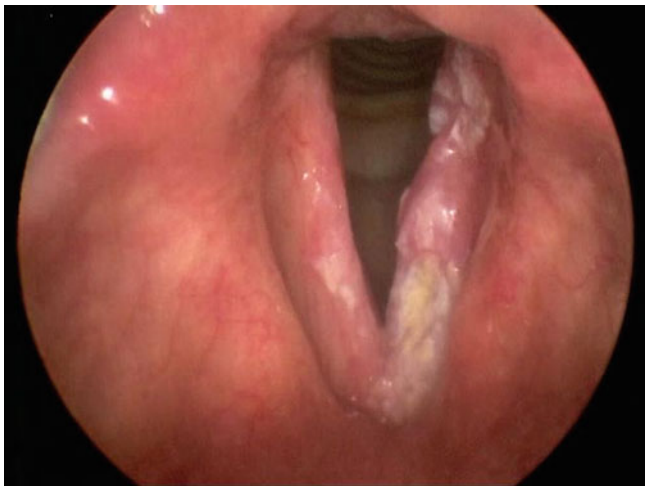

Fig. 14.5 Keratosis

Key Points

- The comprehensive voice evaluation involves several components including a voice-specific history, perceptual auditory evaluation, visualization of the larynx in motion, stroboscopic evaluation, and aerodynamic and acoustical analysis.
- Members of a multidisciplinary voice care team involves laryngologists and speech and language pathologists with voice-specific training and can include other professionals such as vocal coaches, teachers, pedagogues, as well as medical specialties.
- Quality of life and self-assessment tools are an important component of the voice history.
- Image quality is important in evaluating vocal anomalies, and the examiner should choose the best available instruments for evaluating anatomic and functional components of the phonatory cascade.
- Videostroboscopy allows for the assessment of mucosal wave or vibratory function of the vocal folds.
- Flexible nasopharyngeal endoscopy enables visualization of the larynx in a more natural posture during complex phonatory tasks.
- Instrumental analysis of voice including aerodynamic and acoustical analysis provides quantifiable tools to the laryngologist; however, no perfect value or test exists. Careful history taking and clinical evaluation are still the most important tools toward diagnosis.
- Voice problems can be the result of anatomic and physiological disruption of the mucosal wave as well as motion abnormalities of the larynx.
- Functional voice disorders are very common and are usually the produce of elevated tension and strain in the larynx.
- Phonotraumatic lesions typically occur on the middle third of the vocal fold called the striking zone. This area corresponds to the location of maximal velocity and amplitude of the mucosal wave. Lesions that occur outside of the striking zone need a higher degree of suspicion.
- Motion disorders of the larynx including vocal fold paralysis and paresis, vocal fold fixation from disruption of the cricoarytenoid joint, and neurological problems.

Suggested Reading

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Conventional Biopsy Techniques

15

Stefano Gasparini

Introduction

One of the main goals of diagnostic bronchoscopy is to obtain a cytohistological assessment of bronchial, pulmonary and hilar-mediastinal lesions. In order to attain this objective, several sampling instruments can be used through the flexible bronchoscope, depending on the morphology and location of the pathological process. The term "conventional biopsy techniques" implies all those traditional sampling techniques that can be used without adopting the latest technology. In this chapter, conventional biopsy techniques will be divided on the basis of the location of the lesion, analysing methods used for sampling central endobronchial lesions, peripheral pulmonary lesions or lung parenchyma and the pathological processes of the hilar-mediastinal area (Table 15.1).

Central Endobronchial Lesions

Central endobronchial lesions (i.e. lesions located within the visible range of flexible bronchoscope) can be approached for sampling cytohistological material, using forceps biopsy, brushing, washing or transbronchial needles.

Forceps biopsy is the most frequently used sampling instrument by bronchoscopists in airway lesions that can be endoscopically visualised. Different sizes and kinds of forceps are currently available on the market: with a cutting or serrated edge (alligator), fenestrated (to reduce tissue-crushing artefacts), with elliptically or spherical-shaped cups and with a needle between the cups (to prevent slippage of the forceps in case of lesions located on the side tracheal or bronchial wall) (Fig. 15.1). There are no comparative studies that clearly demonstrate the advantages of one kind of forceps over the others for sampling central endobronchial lesions, and even the role of forceps size on the diagnostic yield of bronchoscopically visible tracheobronchial tumours has not been evaluated. Therefore, the choice of forceps is generally based on the operator's experience and preference. Recently, a new commercially available electrocautery biopsy forceps ("hot forceps") was used for sampling endobronchial lesions, with the aim to prevent bleeding. Even if "hot forceps" do not have a negative impact on the quality of specimens, there is no evidence that they may reduce the incidence of clinically relevant bleeding episodes, and their routine use is not warranted.

In order to perform a biopsy of an endobronchial lesion, the forceps must be opened just above the lesion, advanced and pushed towards the area to be sampled, firmly closed and then withdrawn through the working channel of the bronchoscope. The forceps should not be kept too far from the tip of the bronchoscope since, in this way, it is difficult to apply pressure and to maintain contact between the cups and the lesion (Fig. 15.2).

The major advantage of forceps biopsy is the possibility of obtaining specimens suitable for a histological evaluation, while the limitation of this tool is the difficulty in sampling submucosal or peribronchial lesions or in retrieving diagnostic tissue from lesions with a large necrotic component.

When necrotic tumours are encountered, multiple biopsies should be carried out until surface bleeding is visible and viable tissue is obtained.

In central airway lesions, forceps biopsy yields sensitivity that ranges from 74% to 80%, based on the results of two meta-analyses, but there have been studies reporting values higher than 90%. It has been shown that the best diagnostic yield can be obtained by performing three or four biopsies and that the sensitivity does not significantly increase even if more samples are obtained. To improve the diagnostic yield of forceps biopsy, some alternative methods to treat the sample were proposed, such as smearing the biopsy on a slide

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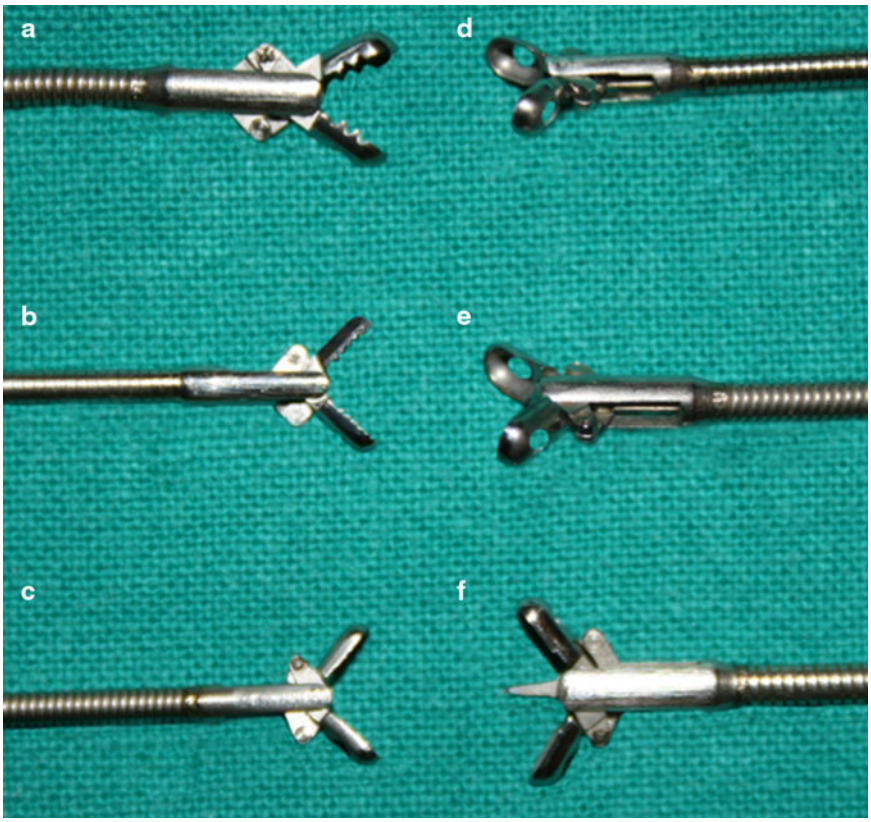

Fig. 15.1 Different kinds of forceps biopsy. (**a**–**b**) Different size alligators (serrated edge); (**c**) elliptical-shaped cups with cutting edge; (**d**–**e**) fenestrated cups with cutting edge; (**f**) with a needle between the cups

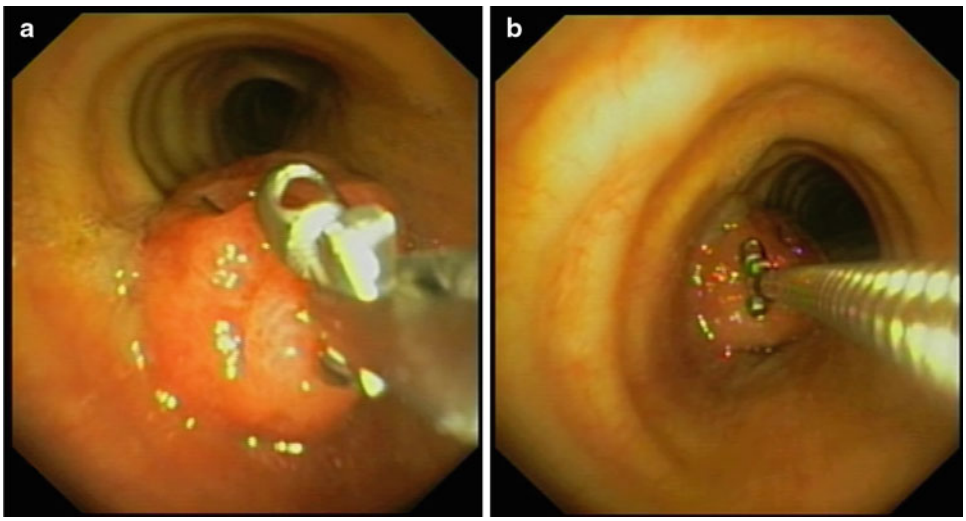

Fig. 15.2 Biopsy of a polypoid lesion obstructing the orifice of the left main bronchus. (**a**) Correct position: the cups are open and the forceps are pushed towards the lesion. (**b**) Wrong position: the forceps are kept too far from the tip of the bronchoscope

(imprint cytology) or cytologically examining the biopsy rinse fluid, but these techniques have not been validated and their use is not recommended.

Bleeding is the most common complication of bronchial biopsy. Generally, bleeding is mild or moderate, and its spontaneous resolution occurs in most instances. Even though it is rare, however, bronchoscopic biopsy-induced bleeding could be life threatening when vascular lesions are approached. Risk factors predisposing to this complication may be related to a variety of coexisting conditions inducing coagulation disorders and/or platelet dysfunction, either as a consequence of underlying systemic disorders (haemorrhagic diathesis, uraemia, haemopathies, liver diseases, immunosuppression) or secondary to medications (anticoagulant therapy, clopidogrel, chemotherapeutic agents). The identification of risk factors and, when possible, their correction is the first step to prevent bleeding. Prebronchoscopy routine coagulation screening is unnecessary in patients with

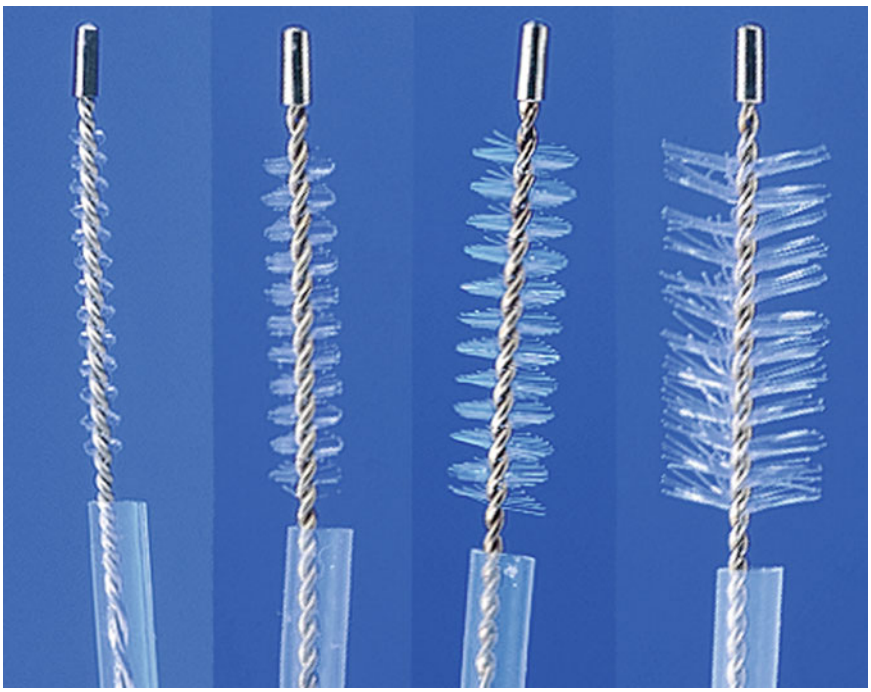

Fig. 15.3 Brushes with plastic sheath of different sizes

no risk factors, but it should be performed in those with known or clinically suspected risks. Bronchial biopsies cannot be performed if platelet count is <50,000/mm^3, and these patients should receive six to ten packs of platelet transfusion before bronchoscopy. Oral anticoagulants should be stopped at least 3 days before bronchoscopy, or low-dose vitamin K should be administered to reduce the international normalised ratio (INR) to <2.5. The use of clopidogrel should be stopped 7 days before bronchoscopy. The risk of bleeding may be also related to the nature of the lesion. Some tumours, like carcinoids and endobronchial renal metastases, are hypervascularised and more prone to bleed, but this is not a contraindication to biopsy.

In any case, bronchoscopists should be trained to manage major bleeding when a bronchial biopsy is performed. The first manoeuvre is to rotate the patient in a lateral decubitus with the bleeding side down. This is a simple and easy procedure that could be life saving, since it avoids the inundation of the contralateral lung. Following the positioning of the patient on the lateral decubitus, the bronchoscope must be kept in site, and continuous suction should be applied to prevent spilling of blood to distal airways, avoiding to keep the tip of the instrument too close to the bleeding lesion. Even if there are no controlled studies that demonstrate the real efficacy of the instillation of ice-cold saline and of epinephrine (diluted in a 1:10,000 mixture of normal saline and administered in 2–3 ml aliquots to a maximum of three doses), all the bronchoscopists agree that these manoeuvres may reduce bleeding and that they should be applied. If the source of bleeding is visible and well localised, the use of low-energy laser or of electrocautery with argon plasma may be helpful. If such procedures are ineffective and a major bleeding continues, the intubation of the patient should be considered using a rigid bronchoscope (if it is available and if there is skill and expertise to its use) or a large channel endotracheal tube, to allow the passage of the flexible bronchoscope. The persistence of bleeding may induce to perform a selective intubation of the contralateral main bronchus to isolate the non-bleeding side, using a normal tube or a Carlens device. Bronchial artery embolisation and open surgical procedures could be considered as a last resort, if all the above-mentioned procedures have failed to stop the haemorrhage.

Brushing is a sampling technique which is widely used by bronchoscopists to collect cytological material from bronchoscopically visible lesions of the airways. There are brushes of different sizes (Fig. 15.3), with or without a plastic sheath, but no differences in diagnostic yield have been demonstrated using different types of brushes. Even if disposable or reusable brushes are available on the market, it is recommended to use disposable tools in order to reduce the risk of contamination or cross infection. Some authors suggest that better cytological material can be obtained when the unsheathed brush and bronchoscope are withdrawn together in order to reduce the loss of material during the passage of the brush in the working channel of the instrument, but other studies have not found any statistically significant improvement in diagnostic sensitivity using this technique.

Material obtained by brushing can be processed by directly smearing the brush onto a glass slide or by inserting the brush into a saline solution and removing the cells by shaking it vigorously. There are no studies that demonstrate the real advantage of one processing technique over the other.

The limitation of brushing consists in being able to sample only cytological material and only from the superficial

layer of the mucosa. As such, this type of instrument is not indicated for submucosal or intraparietal lesions. The advantage of brushing compared to performing a biopsy could consist in obtaining cells from a larger area of the mucosa. The average diagnostic yield from brushing is lower compared to forceps biopsy, with a sensitivity ranging from 59% to 72%. Several authors affirm that by using brushing and biopsy together, diagnostic sensitivity increases and in about 8% of the cases, brushing alone is diagnostic. However, these results are generally reported by non-randomised retrospective studies, performed when the histological characterisation of non-small cell lung cancer was not necessary for therapeutical purposes. In an era of personalised therapy for non-small cell lung cancer, it is important to distinguish between squamous and adenocarcinoma, and it is necessary to obtain an adequate amount of cells or tissues to perform molecular markers-based assessment for guiding therapeutical strategies. Furthermore, while in the past the use of reusable brush did not greatly influence the cost of the procedure, the employment of disposable brush that is recommended today to reduce infection risks could have an economical impact that should be taken into consideration while evaluating the cost-effectiveness of the procedure. In fact, there have been no controlled studies recently that demonstrate the real efficacy of a routine use of biopsy and brushing together in central endobronchial lesions that involve the mucosa. We agree with some authors who hypothesise that the majority of cases which involve the mucosa, where cytology is positive but biopsy is not diagnostic, are a consequence of a non-optimal biopsy sampling technique (wrong forceps positioning, crushing artefacts, necrotic tissue).

Complications resulting from the brushing of central bronchial lesions are very rare. Bleeding and breaking of the brush in the airways have been reported mainly when a reused brush is used.

Bronchial washing is another widely used conventional means of sampling cells from central airway lesions. It can be easily performed by instillation through the working channel of the bronchoscope of about 20 ml of saline that is retrieved by suction. There has been a controversy concerning the optimal timing of washing, when done in association with biopsy (i.e. before or after biopsy), but a more recent prospective study was unable to find any difference in the diagnostic yield for washing before or after biopsies or brushing. The limitation of washing consists in obtaining a sample just by exfoliating superficial cells of the mucosa. The sensitivity of washing for central lung cancer is lower than that obtained by biopsy or brushing, ranging from 29% to 76%, with an average value of 47%. In studies where biopsy, brushing and washing were utilised together, the number of patients diagnosed by washing alone was very small (2.2–3.9%), making the value of the routine use of washing in central bronchial lesions questionable. Since the cost of washing is mainly related to the processing and evaluation of specimens, some authors suggest to collect the washing fluid during bronchoscopy and to hold it in the laboratory, examining the sample only if the other specimens are not diagnostic.

The samples collected by brushing and washing can also be submitted for microbiological evaluation in the suspect of infectious conditions. For this purpose, brush should be agitated in a sterile medium, and washing must be collected in a sterile specimen trap. Even if these specimens are contaminated by oropharyngeal flora during transnasal or transoral passage of the bronchoscope, the value of brushing and washing in the diagnosis of infections has been validated by several studies both in the immunocompetent or immunocompromised patients. The material obtained can be evaluated for bacterial, fungal or mycobacterial smears and cultures. The sensitivity of brushing and washing for the diagnosis of mycobacterial diseases is very high, and it has been reported to range from 58% to 96%. However, routine bronchoscopic samplings for mycobacterial organisms on all patients undergoing bronchoscopy are not recommended in areas not endemic to the disease.

Among the conventional biopsy techniques employed for sampling central bronchial lesions, transbronchial needle aspiration (TBNA) must also be included. The transbronchial use of flexible needles has been introduced for the bronchoscopic approach to hilar-mediastinal lymph nodes located outside the tracheobronchial wall, but this device has also been used for sampling peripheral nodules and central airway lesions (Fig. 15.4). The main advantage of TBNA in bronchoscopically visible lesions is the possibility of the needle to penetrate the deep layers of the mucosa and the peribronchial area, allowing to sample even pathological processes with the intraparietal or submucosal component (Fig. 15.5). Other advantages of TBNA are the following: (1) lower traumatic effects and decreased risks of bleeding, especially for highly vascularised tissue; (2) possibility to sample material from infiltrative lesions covered by hard mucosa, where it could be difficult to obtain specimens with forceps biopsy; (3) better possibility to sample diagnostic cells from highly necrotic lesions, where the needle, bypassing the necrotic component, could collect vital cells from the deeper part of the process (Fig. 15.5) and (4) capability to precisely define the point of sampling, as some time is required during the presurgical staging of lung cancer, in order to accurately define the limit of the tumour. The major disadvantage of TBNA is the price of the needle. Being disposable, it significantly increases the entire cost of the procedure.

The sensitivity of TBNA for central bronchial lesions is reported to range from 68% to 91%, with values similar to those obtained by forceps biopsy. Several studies have shown that the use of TBNA in addition to other sampling techniques

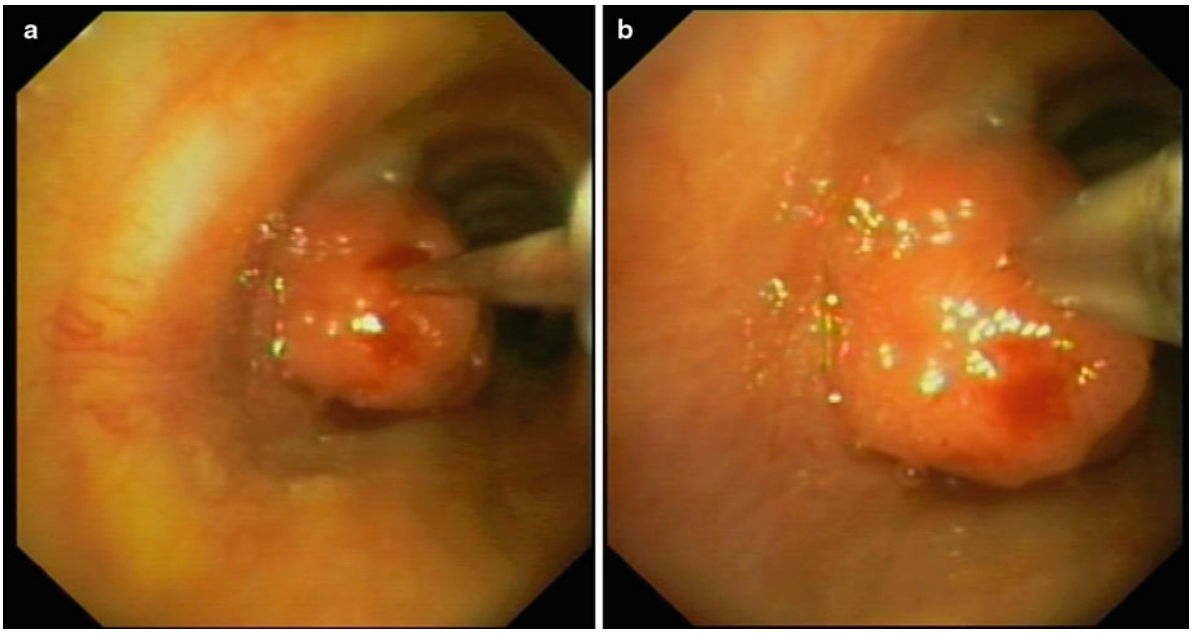

Fig. 15.4 Transbronchial needle aspiration of a central endobronchial lesion. (**a**) The needle is pointed at the lesion; (**b**) the needle penetrates the lesion up to the hub of the sheath

Fig. 15.5 Schematic representation of a necrotic lesion with prevalent submucosal component. The needle is able to penetrate the deep layers of the mucosa and has a better possibility of sampling diagnostic material

for central lesions significantly increases the diagnostic yield of bronchoscopy and that TBNA may be the only diagnostic sampling instrument in a percentage of cases that in some studies approaches 20%. This is particularly evident in studies where cases with submucosal-peribronchial lesions have been analysed. In fact, the use of forceps biopsy together with TBNA seems to be the most appropriate integration for sampling central bronchial lesions which allows to obtain specimens at different levels of the bronchial wall, from the surface to deeper layers, to the submucosa and peribronchial area. However, prospective studies that analyse the cost-effectiveness of this association on a large series of patients are lacking, and there is no evidence that justifies the increase in costs due to the routine use of TBNA along with biopsy in all central airway lesions. In our practice, the use of TBNA is limited to the following: (a) cases with a bronchoscopic pattern suggesting submucosal or peribronchial involvement; (b) cases when the macroscopic appearance of the lesion suggests a very vascularised tissue, to test the bleeding risk before performing biopsy; (c) cases where there is a large necrotic component, and the macroscopic pattern of the biopsy shows white samples suggesting necrotic tissue and (d) repeated bronchoscopy, after a first negative bioptic procedure.

In conclusion, conventional biopsy techniques provide a high diagnostic yield in central airway lesions, and they must be considered the gold standard for diagnosis when an endobronchial pathology visible by bronchoscopy is present. Biopsy forceps provide better sensitivity compared to other sampling techniques when the pattern of the lesion suggests mucosal involvement. TBNA should be the preferred sampling instrument when there is evidence of a submucosal or peribronchial spread of the pathology and when the superficial layers of the mucosa may not be involved or when the lesion is very necrotic. Adding brushing to biopsy or TBNA might

Table 15.1 Conventional bronchoscopic sampling instruments used for lesions of the central airways, for peripheral pulmonary lesions and for pathological processes of the hilar-mediastinal area

Central endobronchial lesions
– Forceps biopsy
– Brush
– Bronchial washing
– Transbronchial needle aspiration
Peripheral pulmonary lesions
– Forceps biopsy
– Brush
– Curette
– Bronchoalveolar lavage
– Transbronchial needle aspiration
Hilar-mediastinal lesions
– Cytology transbronchial needle aspiration
– Histology transbronchial needle aspiration

improve diagnostic yield, but more prospective studies are necessary to evaluate the cost-effectiveness of its use. Washing alone is of little value in the diagnosis of central airway tumours. It may improve the diagnostic sensitivity of bronchoscopy by a small percentage when used together with other sampling instruments, but its routine use is not recommended. Considering the new targeted therapies for lung cancer, future studies should also evaluate the capability of different techniques in differentiating the tumour histotype and in sampling material which is adequate for molecular assessment.

Peripheral Pulmonary Lesions

Different biopsy instruments can be inserted through the working channel of the flexible bronchoscope and pushed into the peripheral airways for sampling cytohistological material from pulmonary lesions located outside the visible range of the bronchoscope (Table 15.1). This kind of procedure can be performed either without means of a guidance system, as in cases of diffuse lung diseases, where it is not necessary to precisely identify the point of sampling, or, in the case of localised pulmonary pathology (nodules, masses or infiltrates), with the use of systems able to visualise the position of the sampling instrument and to assure that the biopsy is performed just in the lesion. Even if new technology can be used for guiding the transbronchial approach to peripheral pulmonary lesions (electromagnetic navigation systems, endobronchial ultrasounds), the conventional and most widely used guidance system remains fluoroscopy. A rotating C-arm or a biplane fluoroscope must be available to allow the assessment of the sampling instrument position both in the anteroposterior and lateral view (Fig. 15.6a, b). Biplane control is necessary to avoid the misplacement of the instrument in front of or behind the lesion. From a technical point of view, after wedging the tip of the bronchoscope into the segmental bronchus that is supposed to lead into the lesion, the sampling instrument must be inserted. At this point, we suggest that the operator look at the fluoroscopic screen rather than at the bronchoscopic monitor and try to direct the sampling instrument towards the lesion by bending or rotating the tip of the scope to find the most appropriate way that leads to the target. If a transbronchial needle is used, the sheath should be flexible enough to be inserted into the most angulated bronchi, like the apical segments of the upper lobes. In our experience, the most appropriate needles for the peripheral lesion approach are those with a metallic sheath that are very flexible and remain straight after insertion, maintaining direction without bending (Fig. 15.7).

The sensitivity of the transbronchial approach to peripheral pulmonary lesions under fluoroscopic guidance varies greatly in the literature, from 22% to 83%, with an overall value of 78%. The major reasons that may explain this diagnostic yield variability are the size of the lesion, the kind and the number of the sampling instruments used, the distance of the target from the hilum and the relationship between the lesion and the airways.

All studies show a strong correlation between the size of the peripheral lesion and the diagnostic results of the fluoroscopic-guided bioptic approach. A sensitivity ranging from 5% to 64% is reported for nodules less than 2 cm in diameter, from 30% to 75% for nodules greater than 2 cm, and this value may increase to over 80% for masses greater than 4 cm.

Concerning the sampling instruments, the majority of the studies performed on the fluoroscopic-guided bronchoscopic approach to peripheral pulmonary lesions show that transbronchial needle aspiration provides a better sensitivity for malignancy in comparison to that obtained with forceps biopsy or brushing. When associated with other means of sampling, the exclusive yield of the needle is reported to range from 8% to 35%. These results could be consequent to the possibility of the needle to also penetrate lesions that do not involve the surface of the mucosa or are located in the peribronchiolar area, where forceps biopsy or brushing cannot be diagnostic. On the contrary, for benign lesions, biopsy forceps seem to provide a better diagnostic yield in comparison to instruments, like brushing and needles, that allow to sample cytological material only. This is not surprising, since the diagnostic definition of a benign process can be more easily performed on a histological basis than one based on cytological evaluation. All authors agree that the diagnostic yield is also influenced by the number of specimens and by the number of sampling instruments used. There are data that suggest that at least six biopsy specimens should be obtained for optimising the results. Furthermore, the association of more sampling instruments provides better results than those obtained with a single tool. The best association could be the use of the needle which provides the best sensitivity for malignancy, and forceps biopsy

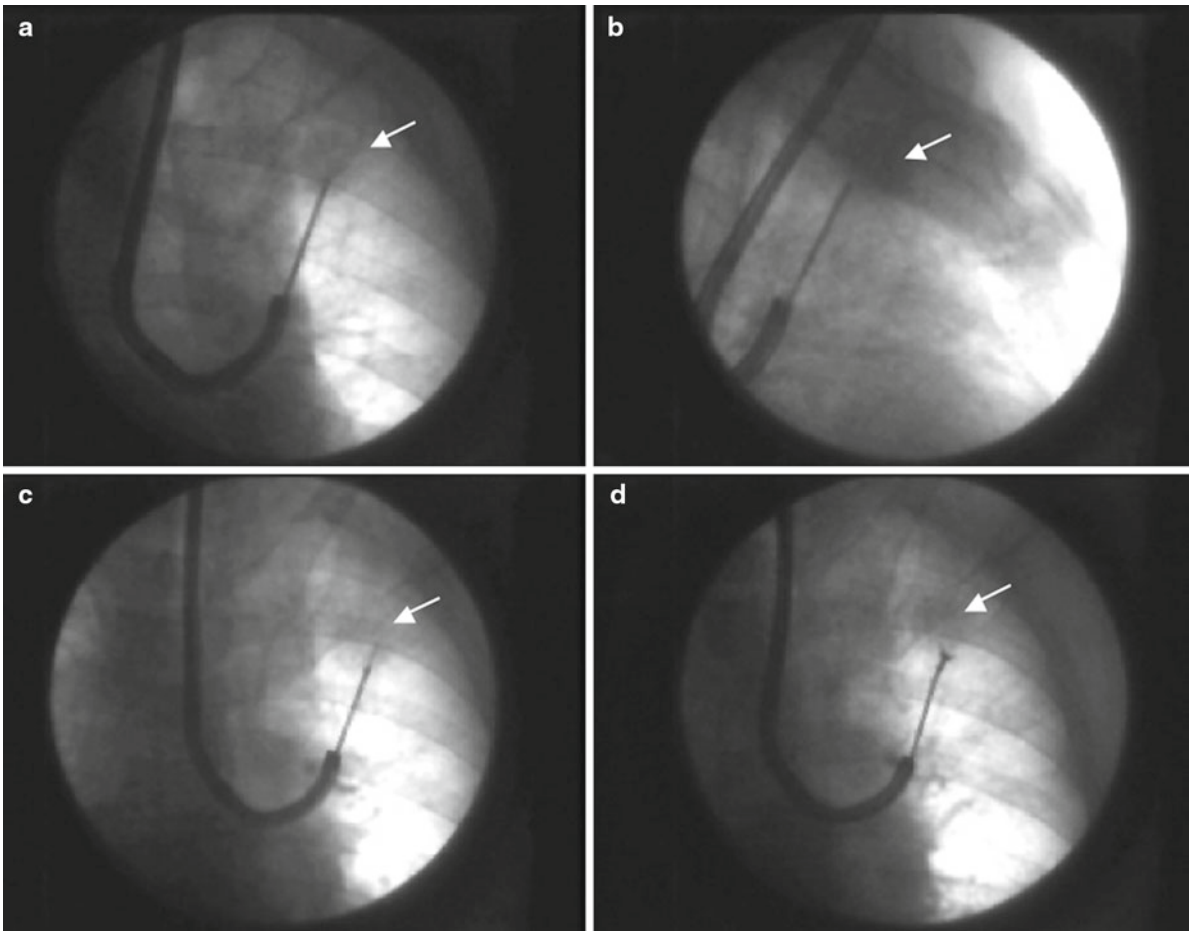

Fig. 15.6 Bronchoscopic approach under fluoroscopic guidance of a 2-cm nodule (*arrow*) of the left upper lobe. (**a**) The sampling instrument is inserted up to the lesion with A-P fluoroscopic control; (**b**) the fluoroscope C-arm is rotated to 90° to assess the correct position of the sampling instrument on the lateral view; (**c**) the needle is extracted from the sheath and suction is applied; (**d**) after needle aspiration, biopsy forceps are inserted into the same bronchus, and biopsies are performed

that is the most appropriate instrument for diagnosing benign lesions (Fig. 15.6c, d). If the needle is used in association with forceps or brushing, it should be used first, since the performance of biopsy or brushing could induce bleeding that may increase the amount of blood aspirated by the needle, thus reducing its diagnostic rate.

The role of forceps size on diagnostic yield of transbronchial lung biopsy has not yet well defined. While some authors report that large forceps yield more alveolar tissue than small forceps, other papers did not find any significant improvement in the diagnostic yield using large forceps. Electrocautery "hot forceps" have also been evaluated for transbronchial pulmonary biopsy. Prospective controlled studies on large number of patients are lacking. From preliminary studies on animal models, it seems that the use of electrocautery hot forceps for transbronchial pulmonary biopsy did not result in improvement of the size of biopsies or collected alveolar tissue.

Bronchial washing or bronchoalveolar lavage (BAL) can also be employed in the case of peripheral localised lung lesions. The advantage of these sampling tools is that they might be used even without the help of guidance systems. However, bronchial washing and BAL alone have very low sensitivity in the case of localised peripheral lesions, with values ranging from 9% to 42%. When performed together with brushing or biopsy, bronchial washing shows an increase in sensitivity by only 3%, which does not justify its routine use. BAL shows better sensitivity in the case of malignancy with an infiltrative pulmonary pattern, like bronchoalveolar carcinoma or lymphangitic carcinomatosis, and its use may be justified if there is a suspicion of these pathological conditions.

Another factor that may affect the sensitivity of the transbronchial approach to peripheral lung nodules is the relationship between the lesion and the bronchial tree. If the lesion is located outside the bronchial system and there is no bronchus leading into it, the chance to obtain a diagnosis using

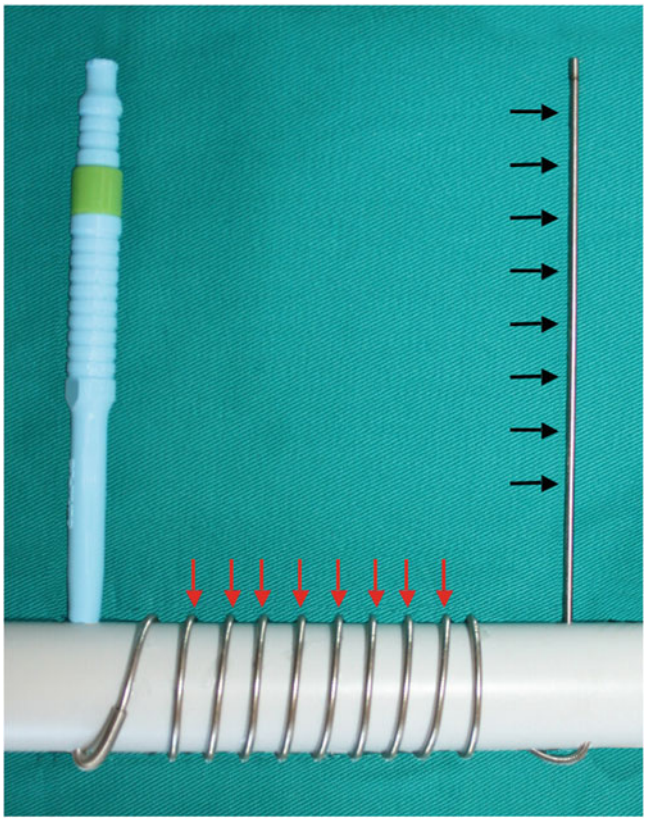

Fig. 15.7 Metallic sheath needle. The flexibility of the needle (*red arrows*) and its capability to remain straight (*black arrows*), maintaining the direction during progression, are shown

the transbronchial approach will be low, whenever a guidance system is used. In this regard, it is useful to evaluate the CT scan "bronchus sign", that is the image of the bronchus leading to or contained within the lesion, visualised by thin-section CT scan, to predict the success of the transbronchial biopsies. Some papers demonstrate that if the bronchus sign is positive, biopsy sensitivity is greater compared to patients without the bronchus sign.

The complications of the transbronchial approach to peripheral lung lesions are not frequent even if its incidence is greater than that reported for central airway biopsy, and the use of forceps biopsy to sample lung parenchyma may slightly increase the risk of bronchoscopy. Most frequent complications are bleeding and pneumothorax. The risk of major bleeding is reported with an incidence of 1–4%, and its rate may further increase in immunocompromised patients, in subjects with uraemia, in ventilated patients, in pulmonary hypertension and in coagulation disorders. The same manoeuvres above reported for the management of bleeding induced by biopsy of centrally located lesions can be also applied in cases of major bleeding after transbronchial pulmonary biopsy. In addition, when bleeding is coming from the airway periphery, an important step is to maintain the tip of the bronchoscope in a wedged position to obtain endobronchial tamponade and to promote the clot formation. Endobronchial tamponade may also be obtained by inflation of balloon catheter (4–7 French), which is introduced through the working channel of the bronchoscope.

The incidence of pneumothorax is reported in about 3% of the patients requiring transbronchial biopsy for diffuse lung diseases. There is no agreement on the possibility of fluoroscopy to reduce the incidence of pneumothorax. However, in the case of localised peripheral lesions, the incidence of pneumothorax after transbronchial biopsy under fluoroscopic guidance is lower and very rare (0.2%).

In conclusion, the conventional transbronchial approach to peripheral localised lesions may be safely conducted using a fluoroscope as a means of guidance, with a mean sensitivity of 78% with lower diagnostic yield for lesions less than 2 cm. In presence of a patient with a CT scan showing a lesion which might be located out of the visible range of the bronchoscope, the operator should be aware that a guidance system (conventionally a rotating C-arm or a biplane fluoroscope) must be available, otherwise the possibility of a diagnosis is very low. Transbronchial needles, showing better sensitivity, should be routinely considered for this kind of procedure. Adding another sampling instrument may increase the diagnostic yield. Since forceps biopsy provides a better capability to define benign processes, the association of needle and forceps biopsy seems to be the most appropriate and recommendable.

Hilar-Mediastinal Lesions

Whilst for bronchial and for peripheral pulmonary lesions there are different bronchoscopic sampling instruments that can be used, the only device available to obtain cytohistological material from lymph nodes or from pathological processes, located in the hilar-mediastinal area, is the transbronchial needle. The term "conventional transbronchial needle aspiration" defines the procedure that is performed inserting the needle at a point of the tracheobronchial tree identified on the basis of CT scan images without the support of endobronchial ultrasound techniques. Some authors define this technique as "blind TBNA" since it is not possible to have a direct image of the lesion and of the tip of the needle once it has been inserted through the bronchial wall. However, since the CT scan provides very accurate images of the location of the mediastinal lymph nodes and of the relationship of the lesion with the tracheobronchial tree, we think that this technique, performed under bronchoscopic visualisation, is not really blind and that the term "conventional" or "standard" TBNA should be preferred.

In the early 1980s, Dr. Ko Pen Wang introduced this technique in clinical practice and published several papers,

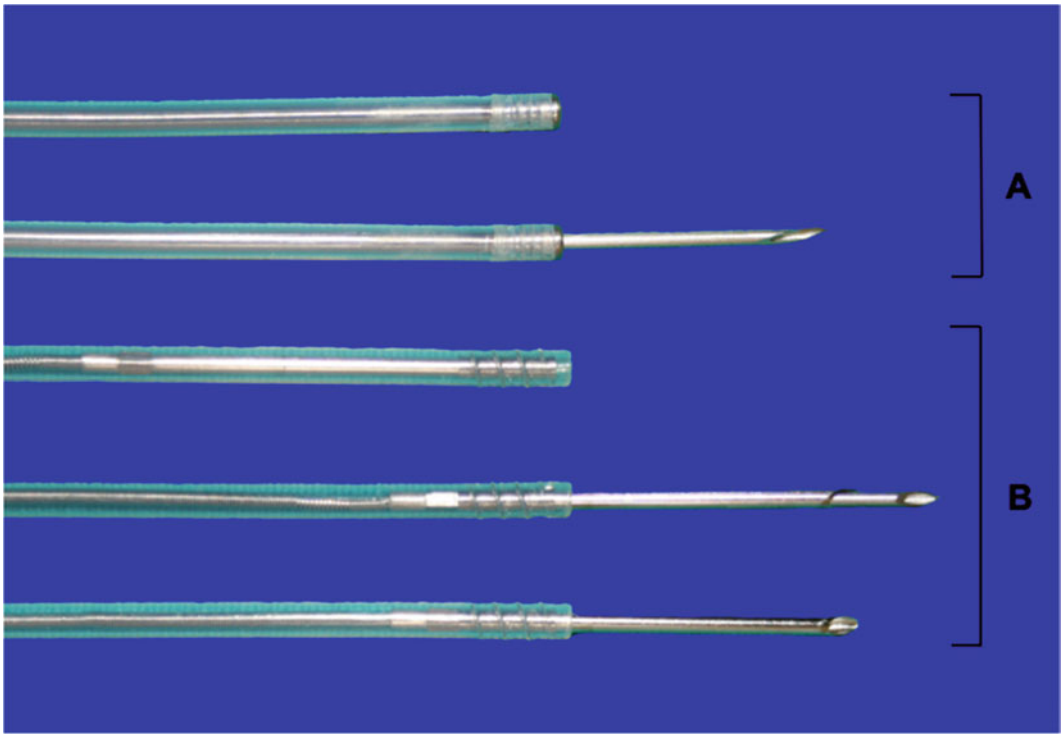

Fig. 15.8 Retractable tips of different kinds of needles for TBNA. (**a**) 21-Gauge cytology needle with the tip retracted (*top*) and extracted from the sheath (*bottom*). (**b**) 19-Gauge histology needle retracted into the sheath (*top*); the dual system made up of an outer cutting 19-gauge needle and an inner retractable 21-gauge needle (*middle*); the 19-gauge needle with the inner 21-gauge needle retracted (*bottom*)

demonstrating the feasibility, safety and efficacy of TBNA both in the staging of lung cancer and in the diagnosis of mediastinal pathology.

Different kinds of flexible needles for TBNA are available on the market, with sizes that go from 19 to 22 G. A TBNA needle for sampling mediastinal lesions should have the following characteristics: (a) a flexible catheter with a proximal control device provided by a port through which suction by a syringe can be done and by a system to manipulate the needle, allowing the exit and the retraction of the tip into the sheath; (b) a tip that retracts into the sheath in order to avoid any damage to the working channel of the bronchoscope during needle progression (Fig. 15.8); (c) a needle length of at least 13 mm in order to allow the tip to progress beyond the tracheobronchial wall and (d) distal end of the sheath that is stiff enough to avoid bendings when the needle is pushed towards the mucosa. Even if metallic sheath needles can be used for sampling mediastinal lesions, the use of transparent plastic sheath needles is advantageous in this procedure since they allow the operator to immediately realise whether blood has been aspirated. While 21 and 22 G needles are proposed for sampling cytological material, 19 G needles are able to provide tissue core for histological evaluation. The most widely used 19 G histology needles have a dual system made up of an outer cutting 19 G needle and an inner retractable 21 G needle, which makes penetration easier and prevents plugging by mucosal material, and which must be retracted after having penetrated the target. Some needles have a lateral hole made with the aim to increase the amount of sampled material, but there is no evidence that this kind of needles provides better specimens or improves diagnostic yield.

The first step towards performing TBNA is to choose the exact point where the needle should be inserted. A careful evaluation of the CT scan allows to identify the location of the mediastinal lesion and its relationship with the trachea or with the bronchi. For each lymph nodal station, well-defined puncture points of the tracheobronchial tree have been described in the literature. Samples can be obtained from right and left paratracheal lymph nodes, retrotracheal, subcarinal, peribronchial and hilar stations (Fig. 15.9). The next steps of the procedure should follow some basic technical shrewdness that are summarised below: (a) Insert the needle into the working channel of the bronchoscope while keeping the instrument as straight as possible and verifying that the tip of the needle is completely retracted into the sheath in order to avoid any damage to the bronchoscope. (b) Extract the needle from the sheath only when the tip of the catheter is visible outside the bronchoscope. (c) Do not keep a long part of the catheter outside the bronchoscope, as it can hinder

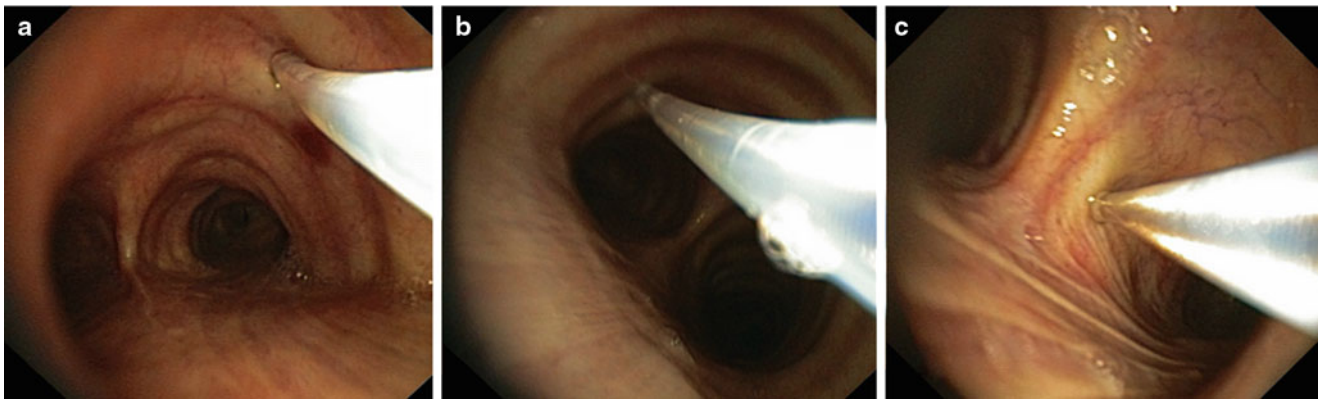

Fig. 15.9 TBNA of: (**a**) Right paratracheal lymph node. The needle is inserted in the second intercartilaginous space above the carina, at 1–2 o'clock; (**b**) left paratracheal lymph node. The needle is inserted at 9 o'clock, at the level of tracheobronchial angle; (**c**) subcarinal lymph node. The needle is inserted in the medial wall of the right main bronchus at 9 o'clock position, at the level of the right upper lobe bronchus orifice

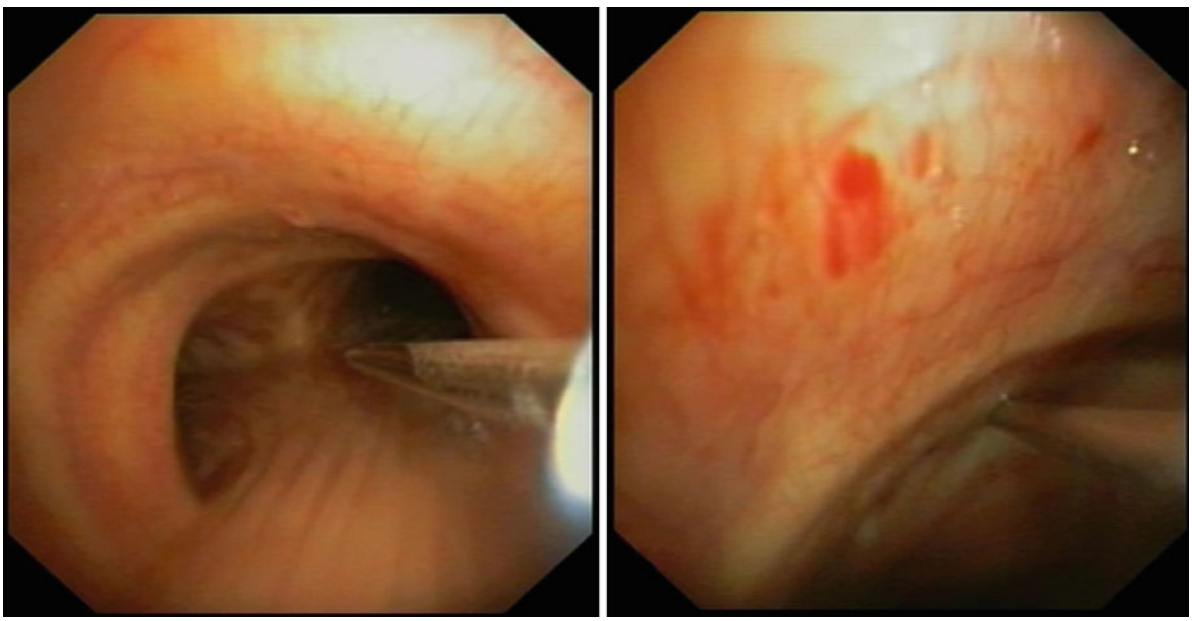

Fig. 15.10 (**a**) The needle has been extracted by the sheath, and it is ready to be inserted. Only the needle and the distal metal hub of the catheter are kept outside the bronchoscope. (**b**) The needle is anchored in an intercartilaginous space, and the tip of the bronchoscope is bent in the same direction as where the needle should penetrate

the movement of the bronchoscope inside the airways. Keep only the needle and the distal metal hub of the catheter outside the scope facilitating the bending, the progression or the rotation of the instrument (Fig. 15.10a). (d) Anchor the tip of the needle in the intercartilaginous space corresponding to the inserting point, and bend the bronchoscope in the same direction where the needle should penetrate (Fig. 15.10b). (e) Insert the needle as perpendicularly as possible through the tracheobronchial wall. In order to obtain a good perpendicular penetration, two main techniques have been described. The first is called the "jabbing method". It is performed by applying a firm and quick jab to the catheter while the scope is fixed. The second technique is called the "pushing" or "piggyback" method whereby the operator fixes the catheter to the bronchoscope at the insertion port of the working channel with his/her little finger or the other hand (Fig. 15.11). The bronchoscope and the needle are then pushed forward together by the bronchoscopist himself/herself using the other hand or by an assistant. There are no studies that demonstrate that one insertion technique is more effective than the other, but in the common opinion of expert bronchoscopists, the "pushing technique" provides a better perpendicular penetration of the needle. Once the needle is inserted and after having verified the complete and correct penetration, suction is applied by the syringe attached at the proximal end of the needle. The catheter is then quickly moved up and down. The aspiration manoeuvre should take no longer than 10 s to avoid the possible coagulation of the blood in the

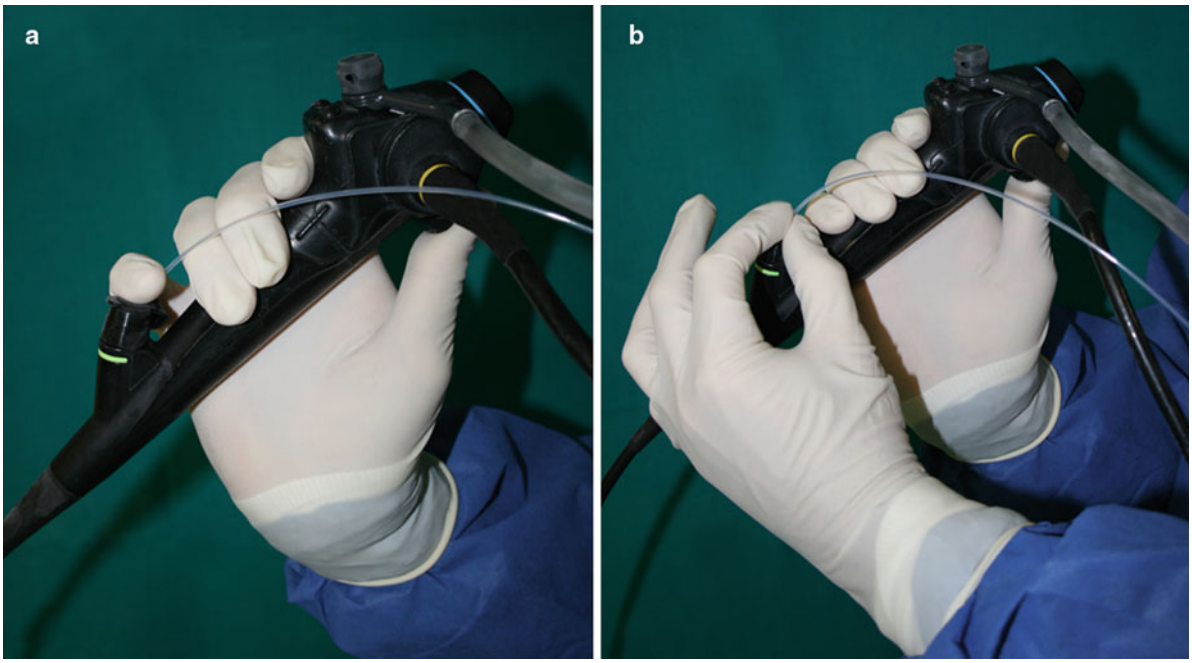

Fig. 15.11 Techniques to fix the needle to the bronchoscope ("pushing" or "piggyback" method): (**a**) with the operator's little finger. In this case, the operator himself/herself can push forward the bronchoscope using his/her other hand. (**b**) With the hand that does not support the bronchoscope. In this case, the bronchoscope must be pushed forward by an assistant

needle. At the end of the aspiration, suction is released, the needle is retrieved into the sheath and the catheter is removed from the bronchoscope.

Another important aspect of the TBNA technique is the proper handling of the specimen. The material is blown by an air-filled syringe onto a slide. It is then smeared using another slide, and immediately fixed in alcohol 95%. If tissue cores are present on the slide, these can be gently removed with a small forceps and put in formalin. By using histology needles, it is possible to empty out the needle directly into a formalin test tube.

The diagnostic yield of conventional TBNA in the staging of lung cancer varies greatly in the literature. However, all papers published after the 1990s generally report values greater than 70%, with a mean value of 78%. Several factors affect TBNA sensitivity, such as size, location and nature of the lesion, number of aspirates performed, type of needle employed, prevalence of malignancy and skill and experience of the operator. TBNA yield increases linearly with the size of the lymph node, from a reported value of only 15% for targets less than 1 cm to about 80% for lesions of 2.0–2.5 cm. For lymph nodes greater than 2.5 cm, the sensitivity does not seem to increase any further. Regarding the site of the lymph node, all authors agree that TBNA of the right paratracheal and subcarinal lesions provides better sensitivity than the sampling of the left paratracheal area. TBNA diagnostic yield also improves with the number of aspirates performed, with an increase in positive results by up to the fourth needle pass. After the fourth aspirate, the sensitivity increases only slightly up to the seventh sample, so that it is recommended to perform at least four aspirates at each lymph nodal station to optimise the yield. Not many studies compare the yield of different types of needles, but some authors report better sensitivity with histology needles compared to cytology needles. Among the factors that affect the TBNA diagnostic yield, the ability and the experience of the operator must also be mentioned. There are some studies that demonstrate how the results improve with practice since performing TBNA requires some specific training and technical knowledge. The discouraging results obtained at very first attempts are the most relevant factor that may explain why this technique has been underutilised for a long time and why still today many bronchoscopists are reluctant to perform it.

TBNA can be performed not only for lung cancer staging but also for the diagnosis of carcinomas that show mediastinal involvement in the CT scan, without any evidence of airway lesions. In such cases, TBNA is the only sampling instrument that allows to obtain diagnostic tissue. In a large series of cancer patients, TBNA is reported to be the only diagnostic tool in 18–35% of cases. Besides lung cancer diagnosis and staging, TBNA may provide cytohistological qualification for all mediastinal pathological processes that are close in contact with the airways. The important role of conventional TBNA in the diagnosis of sarcoidosis has been demonstrated in several studies with a sensitivity greater than 70%, and this technique may improve the diagnostic yield of bronchoscopy by up to 90%, especially for stage I

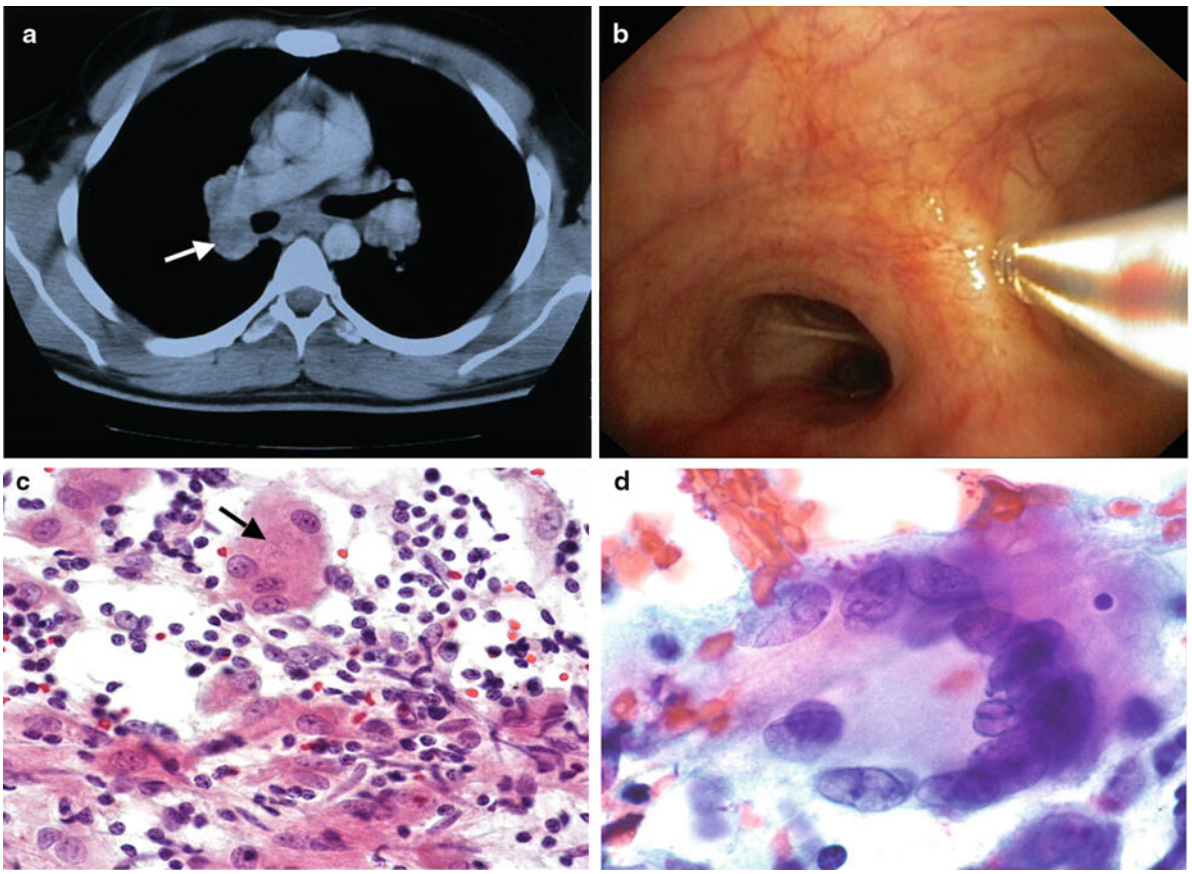

Fig. 15.12 A case of stage I sarcoidosis diagnosed by conventional TBNA. (**a**) CT scan shows lymph node enlargements in subcarinal and bilateral hilar stations. The *arrows* indicate the right hilar lymph node that was punctured; (**b**) the needle is inserted in the spur between the right upper lobe bronchus and the bronchus intermediate; (**c**) cytological specimen showing lymphocytes mixed with epithelioid cells and a multinucleated giant cell (*arrow*) without necrosis (Papanicolaou 40×); (**d**) a large multinucleated giant cell (Papanicolaou 100×)

sarcoidosis (Fig. 15.12). Other pathologies that can be assessed by TBNA are the following: tuberculous adenitis, cryptococcosis, histoplasmosis, lymphoma, thymoma, metastases from mesothelioma, metastases from various extrathoracic tumours and carcinoid.

The specificity of conventional TBNA is very high, ranging from 96% to 100%, and cases of false positive have been very rarely reported. To reduce the risk of possible contamination of the needle by neoplastic cells originating from the airways, the lymph nodes should be sampled before the primary tumour. Puncturing of sites should be avoided where the mucosa is involved by the tumour, and suction should be released before removing the needle from the target lesion.

Despite lack of real-time monitoring of the needle and the possible risk of puncturing large mediastinal vessels, conventional TBNA is a very safe technique, and complications have rarely been reported. Only few cases of pneumothorax, haemomediastinum and major bleeding in the airways have been described. A serious complication arising from TBNA could be damage to the bronchoscope. This risk can be avoided by taking care to introduce and withdraw the needle from the working channel with the tip completely retracted into the sheath.

In the last few years, the advent and diffusion of ultrasound-guided TBNA (EBUS-TBNA) have allowed great improvement in the diagnosis of mediastinal lesions and in the staging of lung cancer. However, conventional TBNA must not be disregarded. In fact, it can be performed during the first diagnostic bronchoscopy and in any bronchoscopic centre even if an echoendoscope is not available. Furthermore, it is advantageous from an economical point of view, not only because the echobronchoscope is an expensive device that has high maintenance costs, but also because the conventional flexible needles are cheaper than the needles for EBUS-TBNA.

In conclusion, conventional TBNA must be included among the routine sampling techniques that every bronchoscopist should be able to perform in order to optimise the diagnostic yield of the bronchoscopic procedures. Hands-on experience and practice on conventional TBNA should be considered as an essential step in training programmes on interventional pulmonology.

Conclusions

Even if the diagnostic possibilities and sensitivity of bronchoscopy have greatly increased by the recent advent of new technological tools, the use of conventional biopsy techniques remains relevantly unchanged and allows the pulmonologist to approach a high percentage of endobronchial, pulmonary and mediastinal lesions for diagnostic purposes. Knowing the possibilities and limits of each and every technique and of its association is a key requirement for choosing the most appropriate sampling strategy, depending on the clinical context and imaging pattern of the lesion. In particular, a careful examination of the CT scan must be the preliminary and fundamental step for planning a bronchoscopic procedure which will allow to identify the characteristics and the location of the lesion so as to be able to decide what kind of biopsy instrument must be used.

Finally, it should be emphasised that, whenever a biopsy technique needs to be employed, its use must always be guided by a global clinical assessment of the patient, evaluating the risk/advantage ratio and the benefits that can be obtained by the procedure case by case.

Only by integrating clinical, imaging and bronchoscopic techniques, it will be possible to optimise bronchoscopy, thereby obtaining the best diagnostic accuracy, minimising the costs involved and having the lowest incidence of risks.

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Bronchoalveolar Lavage

16

Franz Stanzel

Introduction

Bronchoalveolar lavage (BAL) is a low-risk tool, which is very popular, commonly used to get diagnostic information. On the other hand, it may provide prognostic information too.

Among diagnostic tests, BAL has a specific value for the diagnosis of certain interstitial lung diseases (ILDs), such as alveolar hemorrhage, alveolar proteinosis, bronchoalveolar carcinoma, Langerhans' cell histiocytosis, and *Pneumocystis* pneumonia, allowing surgical lung biopsy to be avoided. In other ILDs, BAL findings may support, in combination with clinical and high-resolution computer tomography (HRCT) findings, a suspected diagnosis or make it unlikely. This method is also a valid support for research. Genetic and molecular biomarkers, with different diagnostic/prognostic significance, can be detected in BAL. It has a role in diagnostic of infectious diseases such as bacterial pneumonia, tuberculosis, mycoses, or virus infections of the lung.

BAL Technique

The idea of BAL is to obtain cells, inhaled particles, infectious organisms, and solutes from the lower respiratory tract and from the alveolar spaces of the lung. A sufficient volume of lavage fluid has to be instilled. The minimum is considered about 100 mL of lavage fluid in adults. The recommendations reach from 100 to 300 mL for BAL.

BAL is a minimally invasive technique, which is usually performed during bronchoscopy under local anesthesia and moderate sedation. Local anesthesia is required to avoid cough, but can interfere with the fluid obtained during the process of BAL, and can cause coughing too. The ideal conditions might be under general anesthesia and through the rigid bronchoscope or through an endotracheal tube, but this is far from daily routine. It can be carried out in ventilated patients too.

There have been different guidelines published previously. Though the volume of saline instilled to retrieve cells from the pulmonary parenchyma, the positioning of the patient, the suction applied, and the processing of the BAL fluid for cellular analyses have not been standardized totally, something may contribute to the varying results from different laboratories and centers.

BAL must be distinguished from other lavage techniques. The widely used technique of bronchial washing or bronchial lavage during routine bronchoscopy is different from BAL. It samples material from large airways as trachea and smaller airways down to the level of segmental or subsegmental bronchi for diagnostic purpose as bacteriological or tumor cytology studies. The amount of fluid instilled is comparatively small, around 20 mL. On the other hand, there are therapeutic purposes for lavage techniques too. Often amounts of some aliquots of 20 mL are needed to remove tenacious secretions under bronchoscopy in patients suffering from chronic bronchitis, asthma, or bronchiectasis. This is sometimes necessary and the most simple therapeutic lavage technique. The most invasive lavage technique is whole lung lavage, a therapeutic procedure for pulmonary alveolar proteinosis. It is performed under general anesthesia and double-lumen intubation. Repeated instillations of 1,000 mL are used up to 20 or more liters.

Where to Perform BAL?

The middle lobe or the lingula (or one of its segments or subsegments, if thinner bronchoscopes are used) is recommended as standard site for BAL, if diffuse lung disease is present. From these lobes, about 20% more fluid and cells are recovered than from the lower lobes. Alternatively, one of the anterior segments or subsegments of the upper or lower lobes of both lungs may be used, if it is impossible or difficult to carry

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it out at the standard site. If diffuse lung disease is the indication for BAL, a good interlobar correlation was found concerning lavage cell differentials, lymphocyte subpopulations, and asbestos body counts. While a single-site BAL cellular profile is assumed to be representative of the lung as a whole in interstitial lung disease (ILD), some evidence suggests that this diagnostic procedure might be more useful if it was targeted to one of the pulmonary segments most affected, as identified by chest high-resolution computed tomography (HRCT). In patients with marked radiographic heterogeneity or with localized lesions, such as inflammatory infiltrates, malignant lesions, or from other cause, it is recommended that the area of greatest abnormality, as seen on the chest radiograph or CT, should be chosen as the preferred site for BAL. Some follow the concept of BAL at two or three different sites to reach higher representation.

Instillation and Recovery

The most commonly used instillate is sterile isotonic saline solution (0.9% NaCl). Warming of the instillate to body temperature may prevent coughing and increase cellular yield. The most widespread technique is to instill the fluid directly through the biopsy channel of the fiber bronchoscope. Optimal recovery is accomplished by occluding the bronchial lumen with the bronchoscope. The tip of the bronchoscope is therefore advanced into a bronchial segment (or subsegment) until a wedge position is reached. Alternatively, a suction catheter through the working channel can be used. The catheter is placed more peripherally to subsegmental or subsubsegmental bronchi. Local anesthesia fluid should be removed prior to instillation of the lavage fluid, since it may influence cell viability. The fluid is instilled with syringes using a standard number of input aliquots. Commonly 20-mL syringes are used (alternatively 60-mL) and four to five aliquots are recommended up to a total volume of 100–300 mL. Smaller instilled volumes carry the risk of contamination by the bronchial spaces. Then a more "bronchial" washing component may dominate the cellular picture.

After instillation of each aliquot, the fluid is recovered either by aspirating manually using the attached syringe or by wall suction into a fluid trap. Suction can cause airway collapse and traumatization of the airway mucosa, which may reduce recovery volume and change the fluid profile by adding blood. The optimal effect can be driven by the bronchoscopist by visual control. We prefer the use of 20-mL syringes and instillate the fluid directly through the biopsy channel. A recovery of 40–70% of the instilled volume is normal. The first aspirate may be the smallest one. Reasons for small recovery rates are emphysema, obstructive airway disease, smoking, or a higher age of the patient. Another important reason is a poor wedge position, which leads to leakage and coughing during BAL. Some reject the first "bronchial" aliquot to avoid changes of the following "alveolar" aliquots. Siliconized or plastic containers are recommended to avoid loss of cells through adhesion to glass surfaces.

Safety of BAL

BAL is a minimally invasive technique associated with a low complication rate (0–2.3%) without mortality. Most of the reported side effects are closely related to endoscopic technique, location and extent of lavaged lung area, and the volume and temperature of instilled fluid. Supplemental oxygen delivery throughout the entire procedure, oximetry, and ECG monitoring has been recommended.

The most frequent complications of BAL are transient fever and decrease of lung function parameters. Fever due to resorption of the fluid occurs in up to 30% of the patients. Typically, it occurs some hours after bronchoscopy and is self-limited, resolving within 24 h. Usually there is no need for additional therapy. It depends on the amount of the instilled fluid volume. A transient change of lung function parameters as a decrease of vital capacity, FEV_1, and oxygen tension has been reported. Other side effects are transient alveolar infiltrations. Clinically, wheezing or bronchospasm may be seen after BAL.

Major complications can be seen in patients with severe lung or heart disease. Risk factors for major complications are extensive pulmonary infiltrates, $pO_2 < 8.0$ kPa (<60 mmHg), $SO_2 < 90\%$, $FEV_1 < 1.0$ L, bleeding disorders (prothrombin time <50 s, platelet counts <20,000 platelets/mL), significant comorbidity, and bronchial hyperreactivity. Absolute contraindications for BAL do not differ from those for bronchoscopy.

At the Laboratory

It is essential that the transfer of the materials to the laboratory is performed as quickly as possible, best within 1 h. The next steps recommended are (1) filtration through cotton gauze or nylon mesh, which reduces the mucus and a preferential loss of bronchial epithelial cells without a significant effect on the total cell count and cell differentials, (2) pooling into a single container and measurement of the total volume, (3) centrifugation for 10 min at 500 g, and (4) the supernatant can be stored frozen for subsequent analysis of soluble components.

Routine processing of BAL fluid cellular analyses for patients with ILD includes total and differential cell counts (e.g., counted in a hemocytometer) and the determination of lymphocyte subsets as well as the morphological appearances of cells, besides cultures and special stains for infection in the appropriate clinical setting.

The total count of cells can be performed in a sample of the pooled native fluid or in a resuspension of the cells after the first centrifugation. Washing procedures result in a loss

of total cells but lead to an increase in cell viability of the remaining cells. The total cell count is usually expressed as the total number of cells recovered per lavage but also as the concentration of cells per milliliter of recovered fluid. Cell viability is assessed by trypan blue exclusion and should range from 80% to 95%.

For the enumeration of cell differentials, at least 600 cells are counted on cytocentrifuge or cell smear preparations after staining with May-Grünwald–Giemsa. This number of cells is needed to achieve sufficient reproducibility and low variability in the differential cell counts. The Diff-Quick stain should not be used because it does not stain mast cells. Ciliated or squamous epithelial cells should be noted but not included in the differential cell count. A high percentage of epithelial cells (>5%) is indicative of contamination of the alveolar samples by bronchial cells. Such BAL probes may not be representative for the diagnosis of diffuse parenchymal lung disease. At least three unstained slides should be stored to have the possibility for special staining (iron, periodic acid–Schiff (PAS), silver, toluidine blue, fat, or Ziehl–Neelsen) if clinically indicated or if specific observations arise from the May-Grünwald–Giemsa slides.

If clinically indicated, routine investigations could be expanded by an additional workup. If malignant disease is suspected, the Papanicolaou stain should be added. In case of infection, a complete microbiological assessment, including cultures, should be performed. Lymphocyte subpopulations can be identified by immunocytochemical methods, immunofluorescence, or flow cytometry using monoclonal antibody techniques. The crucial point for flow cytometry is that $\geq 1 \times 10^6$ cells are required to perform an adequate test. These investigations are not recommended as routine procedures for BAL specimens. They are especially indicated in patients with high lymphocyte counts, such as hypersensitivity pneumonitis (HP), or if Langerhans' cell histiocytosis is suspected. CD1a and Langerin are very specific markers for Langerhans' cell histiocytosis. Flow cytometry can be helpful in detecting markers of malignant lymphoma.

In addition, for research purposes, functional studies of viable BAL cells can be performed. The cells can be cultivated in appropriate culture medium, and the release of mediators can be determined along with the mechanisms that appear to regulate the mediator release. It is possible to study cell–cell interactions with co-cultures of two different types of cells. Cells can also be assessed with molecular biology tools to investigate gene activation and intracellular signaling pathways.

As for the measurement of acellular components, a reasonable pragmatic approach was taken by the European Respiratory Society (ERS) Task Force. These components should be expressed as amounts per mL of recovered BAL fluid, in order to facilitate comparison of data from different workers until a reliable external marker can be defined. The report of the ERS Task Force also provides detailed information on the measurement of soluble components.

What Is Normal in BAL?

The BAL fluid obtained from healthy, nonsmoking adults without underlying lung disease is dominated by alveolar macrophages (>80%). Normal in BAL may be 80–90% alveolar macrophages (AMs), 5–15% lymphocytes, 1–3% polymorphonuclear neutrophils, 1% eosinophils, and <1% mast cells.

Cigarette smoking leads to significant effects on BAL samples. The alveolar macrophages from smokers are larger than those in nonsmokers (three- to fivefold increase) and show a characteristic morphology. They contain smoker's inclusion bodies, which are cytoplasmic inclusion bodies consisting of tar products, lipids, lipofuscin, and other substances.

BAL in Different Situations

BAL plays a role in the daily clinical routine in very different situations, as:

- In the diagnosis of diffuse parenchymal lung disease
- In the diagnosis of infiltrations, infectious disease, malignant disease
- An adjunct to diagnosis in different situations
- Assessment of disease activity and prognosis, especially in ILDs

Additionally, it plays a role in research and development of new drugs.

BAL in the Diagnosis of Diffuse Parenchymal Lung Disease

ILDs represent a very broad and heterogeneous group of acute and chronic lung disorders with variable degrees of inflammation and fibrosis. They predominantly affect the distal pulmonary parenchyma including the confined interstitial space bounded by the epithelial and endothelial basement membranes of the alveolar wall. Because of these similarities, they are grouped under ILDs. However, there are significant differences between different ILDs. The etiology, the findings on HRCT and histology differ, as do the clinical course, prognosis, treatment modalities, and response to treatment. Idiopathic interstitial pneumonias (IIPs) are a specific subgroup of ILDs of unknown etiology, with distinct histological features. The initial diagnostic approach includes a full medical history (with occupational and environmental exposures or drug reactions), physical examination, laboratory tests, pulmonary function tests, and imaging (chest x-ray and HRCT). If these noninvasive techniques do not lead to diagnosis, more invasive techniques as bronchoscopy including BAL, transbronchial lung biopsy, and surgical lung

biopsy have to be considered. Among these procedures, bronchoscopy is the least invasive technique. It is generally well tolerated with very low overall morbidity and mortality [19], but there is a discussion, if bronchoscopy is needed.

BAL plays an important role in the diagnosis of patients suffering from pulmonary infiltrates and shadowing and some diffuse interstitial lung disease, so this indication is widely accepted. In most situations, in which diffuse lung disease caused by infectious, immunological, or malignant disease is suspected, BAL should not be considered as the only diagnostic test but in addition to clinical, radiographical, and laboratory tests. The findings of HRCT play a more and more important role. In ILD, the differential cell counts and specific BAL lavage features can be variable, nonspecific, and insensitive. But often, BAL cellular profiles may help to narrow the differential diagnoses of ILDs and to guide further specific diagnostic interventions. However, some BAL findings may be very specific and lead directly to a diagnosis and can in such situations replace biopsy.

Cellular Patterns of BAL

There are different BAL profiles, which are common in the clinical routine. A lymphocytic cellular pattern, a neutrophilic cellular pattern, an eosinophilic cellular pattern, and other inflammatory patterns have different implications (Table 16.1).

A lymphocytic BAL pattern is commonly seen in granulomatous lung diseases, such as sarcoidosis and hypersensitivity pneumonitis (Fig. 16.1a, b), and in the context of immune reactions of the lung to some drugs. However, the number of lymphocytes and the CD4/CD8 ratio can be variable in sarcoidosis. The majority of sarcoidosis cases display

Table 16.1 Diagnosis and BAL

Diagnosis	BAL features
Alveolar hemorrhage	Macroscopically bloody
	Increased intensity from fraction to fraction
	Free red blood cells
	Hemosiderin-laden macrophages
	Fragmented red blood cells in the alveolar macrophages
	≥20% siderophages
Alveolar proteinosis	Milky fluid, PAS + acellular corpuscles
	Foamy alveolar macrophages
	Large amounts of amorphous debris, weak PAS+
Cigarette smoking	Three- to fivefold increase of size of alveolar macrophages
	Inclusion bodies (cytoplasmic inclusion of tar products, lipids, lipofuscin)
Eosinophilic pneumonia	Eosinophils >25%
Hypersensitivity pneumonitis	Lymphocytosis >25%
	Highest lymphocyte count
	CD4/CD8 ratio decreased, but variable too
Infection	Infectious organisms by stains or cultures
Langerhans' cell histiocytosis	CD1a + or Langerin + Langerhans' cells >5%
	Typical smoker's changings
Lipoid pneumonia	Oily material
	Lipid-laden alveolar macrophages
Malignant infiltrations	Malignant cells
Pneumoconiosis	Dust particles in alveolar macrophages
	Birefringent material in alveolar macrophages
Asbestosis	Increased asbestos body count
Sarcoidosis	Lymphocytosis >25%, but milder
	Moderate lymphocyte count only
	CD4/CD8 ratio >3.5 (in the absence of mixed cellular pattern)

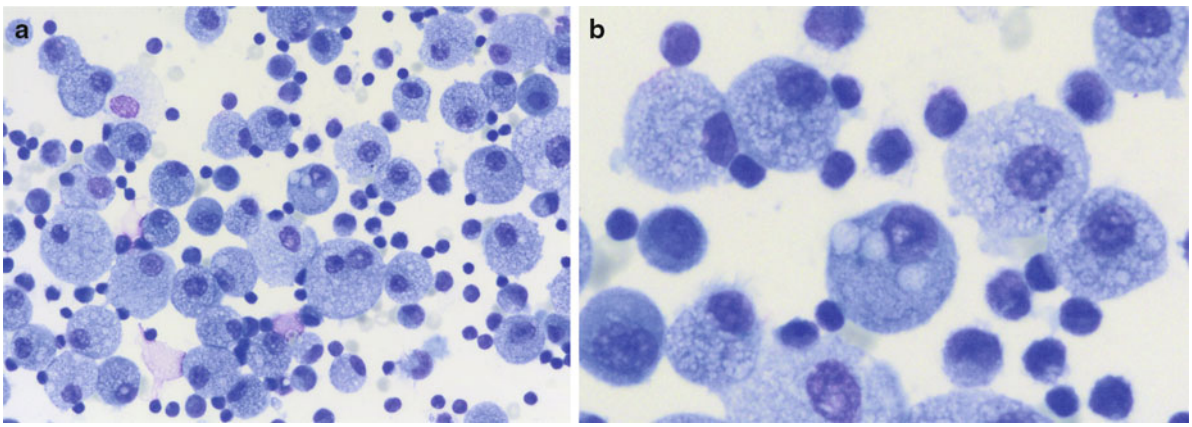

Fig. 16.1 (**a**) Lymphocytic pattern and foamy cytoplasm of alveolar macrophages with vacuoles in hypersensitivity pneumonitis (HP) (Courtesy of Dr. Henry Budihardjo Welim, Institute of Pathology Hemer). (**b**) Vacuoles in alveolar macrophages (Courtesy of Dr. Henry Budihardjo Welim, Institute of Pathology Hemer and Dr. Thomas Beyer, Lung Clinic Ballenstedt)

an isolated BAL lymphocytosis, while a raised neutrophil count appears to correlate with more severe disease and need for therapy. In hypersensitivity pneumonitis, not only the number of lymphocytes but also the absolute neutrophil and eosinophil counts may be significantly increased. BAL lymphocytosis >50% generally raises a suspicion for the diagnosis of hypersensitivity pneumonitis, and patients with hypersensitivity pneumonitis may exhibit either decreased, normal, or increased CD4/CD8 ratio. BAL lymphocytosis may be present in methotrexate and amiodarone pneumonitis, as well as in beryllium disease. BAL lymphocytosis appears to be common in the cellular variant of nonspecific interstitial pneumonia (NSIP) too. Finally, a subclinical lymphocytic cellular pattern in BAL has been reported in Wegener's granulomatosis, Crohn's disease, and primary biliary cirrhosis.

A neutrophilic cellular pattern can be found in idiopathic pulmonary fibrosis (IPF), asbestosis, acute respiratory distress syndrome (ARDS), aspiration pneumonia, subacute hypersensitivity pneumonitis, and cryptogenic organizing pneumonia (COP), as well as in pulmonary infections. An increased neutrophil count may be unspecific but in the appropriate clinical setting is observed in the BAL of 70–90% of patients with IPF. The nonspecific nature of a BAL neutrophilia is illustrated by the difficult diagnostic problem of fibrotic nonspecific interstitial pneumonia (NSIP) too.

An eosinophilic cellular pattern of BAL is in the absence of asthma and parasitic infections highly suggestive of eosinophilic pneumonia. Differential diagnosis may be Churg–Strauss syndrome, allergic pulmonary aspergillosis, drug-induced lung disease, or Langerhans' cell histiocytosis. The diagnosis of Langerhans' cell histiocytosis can be made by the presence of more than 5% Langerhans' cells in BAL, identified by monoclonal antibodies directed against the CD1a antigen or Langerin. Though, it can be an unspecific finding too, as in some cases of IPF, HP, and collagen vascular disease-associated pulmonary fibrosis. If eosinophilia exceeds 25%, eosinophilic pneumonia has to be considered.

Plasma cells are not present in normal BAL. If found, together with foamy macrophages and increased lymphocyte count, HP or drug-induced lung disease has to be suggested. Differential diagnoses are cryptogenic organizing pneumonia and chronic eosinophilic pneumonia. Mast cells appear in the process of lung inflammation and fibrosis. An increased number is sometimes observed in sarcoidosis, associated with advanced or progressive disease.

In addition, if mixed cellular patterns are present, the predominant cellular pattern might offer a hint to the diagnosis, although in these circumstances, invasive procedures such as lung biopsy (bronchoscopic transbronchial or surgical) may be required to make a specific diagnosis.

Specific BAL Findings

In some rare diseases, in the appropriate clinical setting, BAL findings can be diagnostic per se. BAL has a high diagnostic value in these cases (Table 16.2).

Table 16.2 BAL pattern, most important diagnoses, remarks

BAL pattern	Diagnosis	Remarks
Lymphocytic	Hypersensitivity pneumonitis	Highest numbers of lymphocytes
		Highest cell counts
		Lymphocytosis >50%
		Low CD4/CD8 most common
		Foamy macrophages
		Plasma cells may be present (antigen exposure) and transient neutrophil count
	Sarcoidosis	Mostly isolated moderate lymphocytosis
		Neutrophils and mast cells may be present
		CD4/CD8 ratio >3.5, but high variability
		Consider transbronchial lung biopsy
		Consider EBUS-TBNA
	Nonspecific interstitial pneumonia	Cellular variant
		Higher lymphocyte count
		Lower neutrophil count
		Eosinophils may be present
	Cryptogenic organizing pneumonia	Lymphocytes dominantly increased
		Neutrophils, eosinophils, and mast cells increased
		Typical symptoms and radiological findings

(continued)

Table 16.2 (continued)

BAL pattern	Diagnosis	Remarks
	Drug-induced lung disease	Dominance of CD8+ cells
	Silicosis	Dust particles in alveolar macrophages
	Tuberculosis	Staining/cultures for Mycobacteria
		Radiological appearance
Neutrophilic	Idiopathic pulmonary fibrosis	HRCT findings
		Moderate increased neutrophil count (10–30%) in 70–90% of patients
		Eosinophils slightly increased (in 40–60% of patients)
		Neutrophils >2× eosinophils
	Collagen vascular disease	Dominantly increased neutrophils
	Asbestosis	Asbestos bodies (negative in 10–15%)
	Bacterial infection	Bacteria on staining and cultures
Eosinophilic	Eosinophilic pneumonia	Eosinophils >25% (up to 90%)
		Eosinophils > neutrophils
		Plasma cells may be present
		Radiological criteria on HRCT
	Churg–Strauss syndrome	Moderate eosinophilia
	Allergic bronchopulmonary aspergillosis	Staining for Aspergillus+
		Criteria for ABPA
	Drug-induced lung disease	Very variable
Mixed		Predominant pattern may lead to diagnosis

In pulmonary alveolar proteinosis, the BAL fluid looks milky or turbid. Under bronchoscopy, this may cast suspicion on the specific disease. Under light microscopy, the characteristic acellular oval bodies (surfactant-derived lipoproteins) are basophilic on May-Grünwald–Giemsa staining and positive with PAS staining. The background is filled by large amounts of amorphous debris showing weak PAS staining and few foamy macrophages (Fig. 16.2).

The combination of grossly milky BAL fluid, PAS-positive acellular oval bodies, and foamy macrophages under light microscopy is virtually pathognomonic of the disease and obviates the need for transbronchial or surgical lung biopsy.

Pulmonary Langerhans' cell histiocytosis is strongly associated with cigarette smoking, and the BAL differential cytology shows a typical smoker constellation with increased total cell counts and macrophages with smoker's inclusions. The specific finding is an increase in Langerhans' cells to >5% of the total BAL cell count (Fig. 16.3). The sensitivity is low because in late cases of the disease the number of Langerhans' cells decreases in the tissue. Low proportions of Langerhans' cells in the range of 2–4% can be seen in other conditions, such as in healthy smokers, respiratory bronchiolitis/interstitial lung disease (RB/ILD), other ILDs, and bronchoalveolar carcinoma. Staining by monoclonal antibodies for CD1a or Langerin enables identification of Langerhans' cells in BAL (Fig. 16.4). The reaction with the polyclonal antibody S100 is less specific. In cases with characteristic BAL findings, electronic microscopy is not needed.

Multiple causes may lead to diffuse alveolar hemorrhage (DAH). It is a clinical syndrome characterized by severe hemoptysis because of bleeding into the alveolar space. BAL analysis may help to diagnose alveolar hemorrhage syndromes, including Goodpasture's syndrome, Wegener's granulomatosis, systemic lupus erythematosus and other vasculitides, idiopathic pulmonary hemosiderosis, pulmonary capillaritis, and collagen vascular disease. The characteristic findings in BAL are numerous hemosiderin-laden macrophages. If coagulopathy is excluded, BAL is pivotal in excluding or confirming diffuse alveolar hemorrhage in patients with unexplained pulmonary infiltrates. In extensive diffuse alveolar hemorrhage, hemoptysis is often minimal or absent, and HRCT findings are nonspecific.

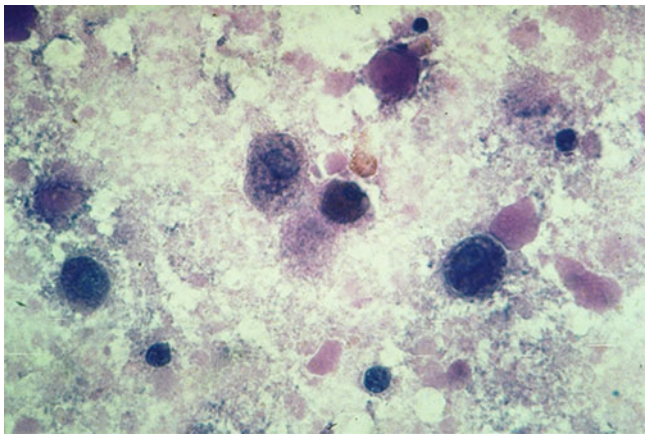

Fig. 16.2 PAS-positive acellular bodies, background filled by debris in pulmonary alveolar proteinosis (Courtesy of Dr. Thomas Beyer, Lung Clinic Ballenstedt)

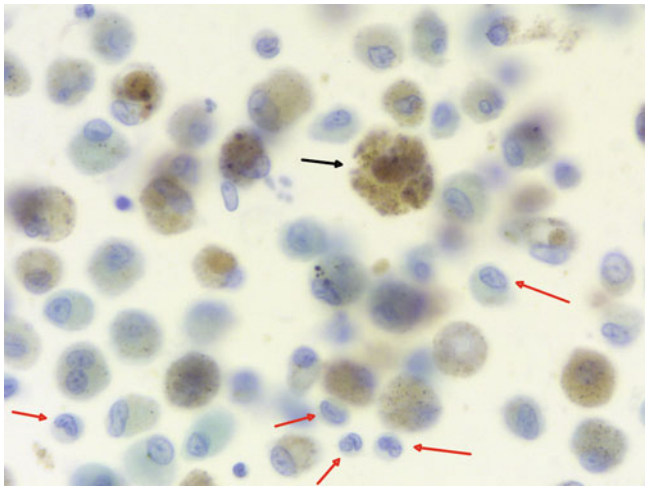

Fig. 16.3 Alveolar macrophages (*black arrows*) with smoker's inclusions and Langerhans' cells in pulmonary Langerhans' cell histiocytosis (*red arrows*). Note the notches of the nuclei of Langerhans' cells (Courtesy of Dr. Henry Budihardjo Welim, Institute of Pathology Hemer)

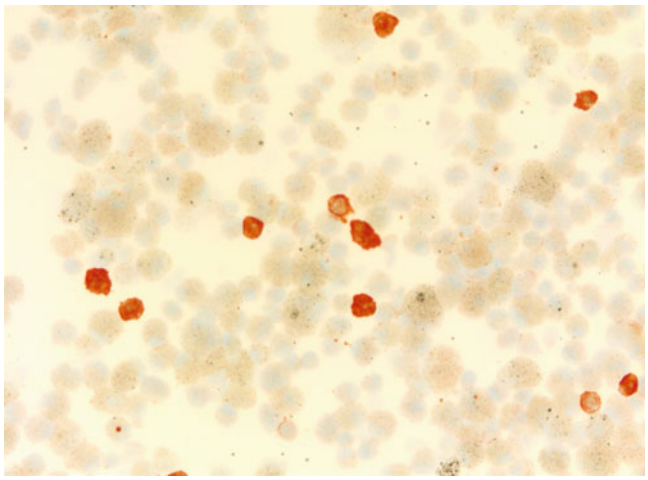

Fig. 16.4 Staining by monoclonal antibodies for CD1a identifies Langerhans' cells (Courtesy of Dr. Henry Budihardjo Welim, Institute of Pathology Hemer)

Fresh bleeding leads to free red blood cells in the BAL fluid. Fragments of ingested red blood cells within the cytoplasm of macrophages are pathognomonic. The color of the BAL fluid is bloody or something between pink and brown, depending on the interval and intensity to bleeding. The recovered fluid stains more intensely from fraction to fraction, which is characteristic for alveolar hemorrhage. It can be distinguished from aspirated blood from the bronchi by the fact that then the first fraction is the bloodiest one.

To assess the severity of bleeding, the percentage of siderophages can be counted. This is more practical than the time-consuming application of the Golde score, which also takes into account the intensity of staining of each macrophage. It has been shown that a percentage of siderophages ≥20% is sufficient for the diagnosis of DAH. Hemosiderin-laden macrophages do not appear earlier than 48 h after bleeding. Thus, very early bleeding shows only numerous red blood cells.

It is important to highlight that many syndromes belong to this group of disorders; therefore, other clinical and laboratory findings must be considered to establish the cause of bleeding. In the clinical setting, chronic left heart failure with pulmonary congestion is one of the most frequent underlying conditions for the finding of DAH in BAL fluid examination.

BAL is not as sensitive for solid tumors as biopsy or other cytology techniques. But diffuse malignant infiltrates can be reliably diagnosed in 60–90% of cases. Malignancies like primary bronchoalveolar carcinoma or lymphangitis carcinomatosis due to adenocarcinoma have the highest yield in BAL. BAL can also provide diagnostic cytological material in hematological malignancies of the lung, including lymphoma, leukemia, and others.

Different pneumoconioses lead to changes which can be detected through the use of BAL. Dust particles in alveolar macrophages can confirm exposure, but no close correlation exists between the extent of disease and the quantity of inhaled dust. Dust particles and birefringent material within the alveolar macrophages or elevated asbestos body counts suggest occupational exposure.

In asbestos-related disease, asbestos bodies can be detected in smears or cytocentrifuged preparations of BAL fluid. More sensitive, however, is the quantification of asbestos bodies by a specific millipore filtration technique (Figs. 16.5 and 16.6). It shows a good correlation with the asbestos body count in lung tissue analysis. A negative BAL asbestos body count does not exclude asbestos-related disease, as 10–15% of subjects with known occupational asbestos exposure do not have detectable asbestos bodies in their BAL fluid.

Chronic beryllium disease is clinically, radiologically, and histologically identical to sarcoidosis. Even BAL lymphocytosis and an increase of CD4/CD8 ratio are identical. Diagnosis can be confirmed by an in vitro lymphocyte transformation test because the antigen is known. The transformation test in BAL is more sensitive and specific than the blood test.

Eosinophilic lung diseases can be diagnosed when there are ≥25% eosinophils in BAL of the radiologically affected segment. In both acute and chronic eosinophilic pneumonia, the fraction of BAL eosinophils ranges from 20% to 90% and is higher than the neutrophils fraction. In addition, a mild-to-moderate increase in lymphocyte count with a decrease in CD4/CD8 ratio can be observed. Sometimes plasma cells can also be detected. Churg–Strauss syndrome shows similar findings. The diagnostic significance of a

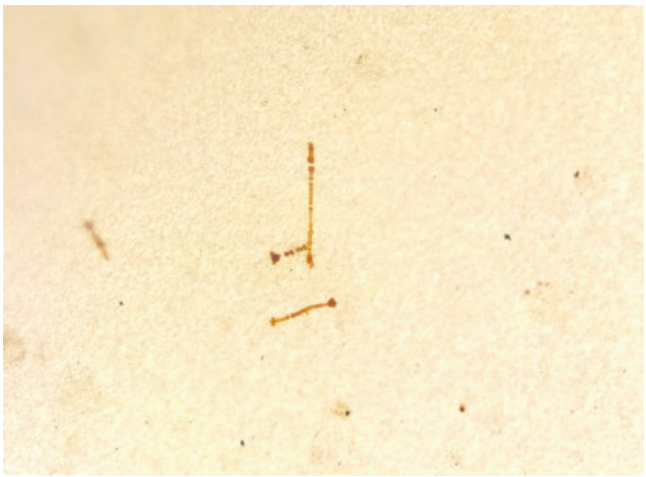

Fig. 16.5 Asbestos bodies by millipore filtration technique (Courtesy of Dr. Henry Budihardjo Welim, Institute of Pathology Hemer)

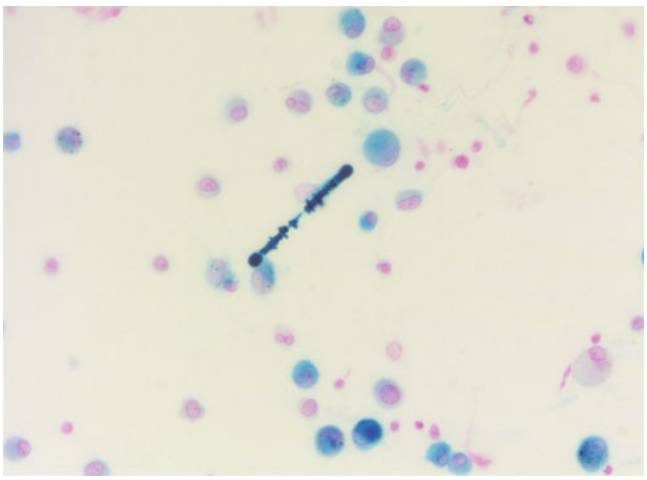

Fig. 16.6 Ferruginous body in the BAL of the same patient (Courtesy of Dr. Henry Budihardjo Welim, Institute of Pathology Hemer)

milder eosinophilia (<20%) is limited since it may be present in ILD or asthma too. In combination with clinical and HRCT findings, eosinophilic lung diseases can be appropriately diagnosed by BAL even without open lung biopsy.

Aspiration has to be considered in the differential diagnosis of recurrent pneumonia or atypical diffuse pulmonary infiltrates. BAL analysis shows usually large numbers of lipid-laden macrophages with marked vacuolization of their cytoplasm. These finding is highly suggestive for lipoid pneumonia caused by chronic aspiration. Other differential diagnoses are hypersensitivity pneumonia and drug-induced pneumonia.

In immunocompromised patients with pulmonary infiltrates, opportunistic infections are common. In this setting, BAL is one of the most important tools. The sensitivity of BAL ranges from 60% to 90% in the diagnosis of bacterial infections; 70–80% in mycobacterial, fungal, and most viral infections; and 90–95% in *Pneumocystis jivorecii* pneumonia. If *Pneumocystis* infection is suspected, the BAL fluid should not be filtered through gauze, as *Pneumocystis* is commonly found in mucous material. The characteristic cysts of *Pneumocystis* can be detected on May-Grünwald–Giemsa or Grocott stained slides. The cysts are foamy vacuoles within an accumulation of slightly basophilic amorphous material. Staining with modified toluidine blue or silver methamine visualizes the cyst wall. There is a high sensitivity of PCR (>90%) for *Pneumocystis jivorecii* in BAL. A positive PCR for *Pneumocystis* should be confirmed by staining methods to differentiate between colonization and infection. In cytomegalovirus pneumonia, the characteristic cytomegalic-transformed cell (the owl eye cell) with typical nuclear or cytoplasmic inclusions is highly specific and can be seen on light microscopy in 30–50% of cases.

BAL as an Adjunct to Diagnosis

Most BAL findings in ILDs are unspecific. However, BAL and cellular analysis may help clearing up a diagnosis. Very important is the context of clinical and especially radiological HRCT findings. BAL cellular patterns can generally differentiate the fibrosing conditions (characterized by neutrophilia and eosinophilia) from granulomatous diseases (lymphocytosis with or without granulocytosis). For further specification, the CD4/CD8 ratio may be helpful. In some centers, CD4/CD8 ratios are considered to be diagnostically useful, with an increased CD4/CD8 ratio favoring a diagnosis of sarcoidosis, whereas a low CD4/CD8 ratio is more usual in HP. But it is clear that there are too many exceptions to these observations. This BAL distinction is not definitive in isolation.

In most of the patients suffering from sarcoidosis, BAL shows a typical pattern, demonstrating lymphocytic alveolitis (>90%) independent of the stage of disease. If there is active sarcoidosis, the lymphocyte counts tend to be higher, but the range is wide. In the more advanced stages, neutrophils and mast cells may also be increased. Even if imaging findings are normal, BAL findings may be typical in sarcoidosis patients.

The CD4/CD8 ratio is characterized by a high variability in sarcoidosis, so it has been debated controversially. At the time of diagnosis, not every patient has an increased CD4/CD8 ratio. Most probably it is increased if acute sarcoidosis or Löfgren's syndrome is present. On the other hand, even 15% of patients show a decreased CD4/CD8 ratio. The sensitivity for diagnosis of sarcoidosis is low around only 55%, but the specificity is high around 95%, higher than the specificity of transbronchial biopsy. Increased neutrophils in BAL of patients with newly diagnosed sarcoidosis may indicate unfavorable prognosis.

The disease showing the highest total cell count and the highest lymphocyte count is extrinsic allergic alveolitis or hypersensitivity pneumonitis (HP). The proportion of lymphocytes exceeds often 50%. The number of activated T cells is also increased. The CD4/CD8 ratio can be decreased, which was a general belief, but it can be normal or increased too. A higher ratio is more probably found in chronic disease.

The alveolar macrophages are heterogeneous and often show a foamy cytoplasm. Plasma cells can be seen in patients with recent antigen exposure. In contrast to sarcoidosis, an increase of neutrophils, eosinophils, and mast cells can also be observed. To complicate matters further, the BAL profile of HP is also heavily influenced by the time that has elapsed from antigen inhalation and the intensity of exposure. Following an acute episode of HP, the neutrophil count may increase transiently. Exclusions for HP are a normal cell appearance and an isolated increase in neutrophil or eosinophil count.

A large number of different drugs may cause drug-induced pneumonitis. The mechanisms are either toxic or immunological. BAL findings are very different. Lymphocytosis, granulocytosis, cytotoxic reactions, and diffuse alveolar hemorrhage can be found, partly combined. The most frequent finding is lymphocytic alveolitis with a dominance of CD8+ T cells. Most important are an increase of CD4+ cells in methotrexate-induced pneumonitis and the presence of alveolar macrophages with a finely vacuolated foamy cytoplasm in amiodarone-induced pneumonitis. If no foamy macrophages are found, amiodarone-induced pneumonitis may be excluded. But these findings are not specific, so diagnosis cannot be made on this only.

Idiopathic pulmonary fibrosis (IPF) is a progressive and often fatal fibro-proliferative lung disorder of unknown etiology characterized by the histopathological and HRCT pattern of usual interstitial pneumonia (UIP). The existing American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement suggests major criteria (exclusion of known causes of interstitial lung disease, abnormal pulmonary function with restriction and/or decreased gas transfer, bibasal reticular abnormalities on HRCT scans or chest radiograph, BAL or transbronchial lung biopsy not suggesting any other disease) and minor criteria (age >50 years, insidious onset of otherwise unexplained dyspnea, duration of illness >3 months, bibasal inspiratory crackles on auscultation) for the clinical diagnosis of IPF. The role of surgical lung biopsy is debated controversially. If a diagnosis cannot be made on the basis of these simple criteria, surgical lung biopsy may be necessary for a confident diagnosis [18]. However, if classical features in HRCT images, which are associated with a UIP histopathological pattern, are present, there will be no need for lung biopsy. In the moment, there is no consensus on the role of BAL and biopsy. Awaited new evidence-based guidelines for managing IPF will clarify the diagnostic process of IPF.

One of the problems with IPF is that the disease has no pathognomonic clinical, biochemical, BAL cellular, or pathological features. The role of BAL in IPF is controversial. In early published case series, the diagnostic value of BAL findings was considered in isolation in groups of patients, without reference to a priori probabilities of individual diagnoses (based on the relative prevalence of individual disorders), the clinical presentation, or findings of other tests. For this reason, these studies failed to quantify the true added diagnostic value of BAL in diffuse parenchymal lung disease. BAL may be useful in individual patients, in altering the balance of diagnostic probability, but is rarely diagnostic itself. A diagnostic likelihood of only 30–70% means major uncertainty. The same reservation applied to the predictive value of CD4/CD8 ratios. The prevailing problem is that no study exists in which BAL data are integrated with the pretest probability of disease, based not only on disease prevalence but also on age, sex, smoking history, mode of presentation, observed disease behavior, observed previous responsiveness to treatment, clinical evaluation, and the results of other tests. The problem has been compounded by the advent of HRCT, which has transformed the diagnostic landscape. The definition of pre-BAL diagnostic probabilities has been refined radically in the HRCT era, and thus, the landmark BAL series of the 1980s are now out of date. A second problem, common to all clinical diagnostic studies, is the issue of an appropriate reference standard.

Although BAL findings are nonspecific to IPF, they differ distinctly from differential cell counts in sarcoidosis or HP. Typically there is a moderately increased neutrophil count (10–30% of the total cells). Eosinophils may slightly be increased too, but neutrophils are usually twice of eosinophils. Seventy to ninety percent show an increased neutrophil count, and 40–60% show an additionally increased eosinophil count. A minority of patients have a moderately increased lymphocyte count too. Conversely, a lone BAL lymphocytosis is an uncommon finding in IPF and, when present, should raise the suspicion of alternative diagnoses, such as granulomatous infectious diseases, sarcoidosis, HP, COP, NSIP, or lymphocytic interstitial pneumonia (LIP). If a marked increase of lymphocytes is found, such diseases have to be excluded. An increase in the BAL lymphocyte count, which has been associated with a positive clinical response to steroid treatment and better outcome, is found in 10–20% of patients with IPF. However, because these latter data come from historical studies, some of these patients most probably had NSIP, a more benign form of idiopathic interstitial pneumonia, which more recently has been conceived as a separate entity.

Conversely, distinguishing IPF from the fibrotic variant of NSIP solely based on the BAL cellular profile is far more difficult. Recently, the role of BAL in separating NSIP from

UIP in a large patient population retrospectively was evaluated. It was found that UIP is characterized by a higher neutrophil count (7%) and lower lymphocyte count (5%) than NSIP (3% and 29%, respectively).

A BAL lymphocytosis with a mild increase in the neutrophil and eosinophil count may be seen in nonspecific interstitial pneumonia (NSIP). Cellular NSIP is more frequently characterized by BAL lymphocytosis than fibrotic NSIP. The BAL findings in cellular NSIP may be similar to those of cryptogenic organizing pneumonia (COP). These results are in contrast with other published data, demonstrating that BAL had neither a diagnostic role nor prognostic value in a smaller cohort of patients with either IPF or idiopathic NSIP. When diagnosis of IPF is based on HRCT, pulmonary function, and clinical findings, in the presence of a predominantly lymphocytic BAL, alternative diagnoses should be suggested. A retrospective analysis on IPF patients data showed that none of them had >30% lymphocytosis, with three patients (7%) displaying only mild lymphocytosis (range 14–17%), far below a discussed 30% cutoff. This data are consistent with previous data showing that an increase in BAL lymphocytes alone may be present in up to 10% of IPF patients only.

First, the clinical entity of NSIP was termed as "provisional." It subsequently became apparent that the term NSIP, as applied over the past decade, covered distinct diverse clinicoradiological profiles, including profiles suggestive of COP, HP, and even IPF. Among these disorders, cryptogenic organizing pneumonia (COP) was described in the mid-1980s, but typical BAL profiles were not at first recognized, and thus, the presence of COP was not considered in the differential diagnosis of a lymphocytic profile. This omission had important implications with regard to reports of the diagnostic and prognostic utility of BAL. The BAL profile of COP, evaluated in a number of studies, includes a lymphocytosis in the great majority of cases, but other cell types (neutrophils, eosinophils, and mast cells) are commonly (although not always strikingly) increased. The eosinophil counts are not as high as in patients with chronic eosinophilic pneumonia, usually less than 25%. The combination of typical clinical symptoms and patchy infiltrates, a BAL cell profile of >20% lymphocytes, eosinophils between 2% and 25%, and a CD4/CD8 ratio <1.0 are highly suggestive for COP if infection or malignancy is excluded. Based on this, a corticosteroid therapy is well founded.

Nonetheless, the early series drew important broad diagnostic distinctions between granulomatous lung disease and IPF. Only a BAL neutrophilia, often associated with an eosinophilia, in IPF and a BAL lymphocytosis, with a variable BAL neutrophil content and, in HP, an occasional BAL eosinophilia, has stood the test of time. However, the use of BAL to make more refined diagnostic subdivisions among the more prevalent diseases has proved disappointing.

The BAL fluid in acute interstitial pneumonia is often bloody and rich in albumin, indicating increased alveolar capillary permeability. The typical cellular BAL finding is a marked increase in neutrophils and an occasional increase in lymphocytes. Atypical pneumocytes mimicking adenocarcinoma and fragmented hyaline membranes may also be observed.

Desquamative interstitial pneumonia (DIP) and RB/ILD are smoking-related ILDs. The typical BAL finding in desquamative interstitial pneumonia and RB/ILD is an increase in macrophages with black pigmented inclusions. An increase in neutrophils, eosinophils, and occasionally, lymphocytes may also be seen.

In collagen vascular disease, pulmonary involvement is frequent and associated with different histological patterns. It may reach from patterns like usual interstitial pneumonia to patterns like nonspecific interstitial pneumonia. The HRCT pattern may show this variability too. The BAL findings vary too and are different to IPF. The general pattern is increased neutrophils, may be together with increased eosinophils, and more likely together with increased lymphocytes, and in different combinations. The NSIP pattern is the more prevalent. Increased BAL neutrophils may be associated with more extensive changes on HRCT. But BAL cell profiles do not seem to be useful to predict survival, progression, or treatment response in systemic sclerosis-associated interstitial lung disease. In general, the BAL profile is nonspecific. BAL plays a greater role in clinical routine of these patients by managing drug-induced pulmonary disease, infection, hemorrhage, and malignancy.

It is debatable in IPF, whether BAL adds diagnostic value to a thorough and very careful history and clinical and laboratory findings, thus highlighting the importance of excluding known causes of interstitial pneumonia at the beginning of the diagnostic process. The diagnostic gold standard of IPF is therefore an integrated clinical–radiological–pathological evaluation.

Assessing the Activity of Disease and Prognosis

The difficulties in relating historical BAL data to diagnosis apply equally to the use of BAL in the definition of prognosis. It is unclear whether BAL cellularity is useful for assessing the activity of disease processes with respect to obtaining prognostic information.

In sarcoidosis, differences were observed for several BAL parameters between clinically active and inactive patient groups, but without predicting long-term outcome in individual patients. In patients with IPF, a BAL lymphocytosis was found to denote a more favorable course, including a higher likelihood of a response to treatment. In contrast, a BAL neutrophilia or eosinophilia was associated with a poor outcome.

A recent analysis of 156 patients showed that an increased BAL neutrophil percentage was an independent predictor of early mortality. It is increasingly accepted that in diffuse lung disease, "diagnosis is prognosis". Thus, it is unclear whether the prognostic value of a BAL lymphocytosis relates solely to its diagnostic value or whether it carries a separate prognostic advantage in patients with IPF, diagnosed using recent criteria. However, after adjustment for underlying disease severity (using pulmonary function tests and HRCT data in separate multivariate models), BAL neutrophil content does not differ between different diseases, which makes it difficult to argue for a tight link between a BAL neutrophilia and the intrinsic progressiveness of disease.

In pulmonary fibrosis due to pulmonary involvement in systemic sclerosis, neutrophilia is the most prevalent BAL abnormality. It is associated with a worse outcome if other data are not considered. However, there is ample evidence that in systemic sclerosis, neutrophilia is linked to more extensive pulmonary fibrosis on HRCT and greater pulmonary function impairment. In one recent study, the presence of a BAL neutrophilia had no independent prognostic significance in a large cohort of systemic sclerosis patients, after adjustment for disease severity. Thus, it appears that in systemic sclerosis, a BAL neutrophilia is no more than a marker of disease severity and the same may also apply to other diffuse lung diseases.

It is not proven that BAL or serial BAL is helping to guide therapy or to predict treatment response. At present, BAL cannot be routinely recommended for this purpose. In general, it appears that the presence of a BAL lymphocytosis or neutrophilia is much less influential in prognostic evaluation than accurate diagnosis and the accurate staging of disease severity, respectively.

BAL in the Diagnosis of Infections

BAL may help to detect infections of the lower respiratory tract. But the role of BAL in this context is debatable too. The material should be processed as soon as possible, thus avoiding further contamination or missing such agents as anaerobic bacteria. BAL fluid should be worked up for bacterial, fungal, opportunistic, and viral infections. In addition, the material should be examined by a cytopathologist. BAL fluid should be stained and cultured quantitatively for bacteria using appropriate media, stained and cultured for mycobacteria (including mycobacteria other than *M. tuberculosis*) and for fungi.

In most clinical situations, there is no advantage for those invasive techniques over less invasive procedures as sputum diagnostic or blind aspirations of the trachea in bacterial pneumonia. In the management of severe community-acquired pneumonia, it could not yet be shown that etiological diagnosis with or without bronchoscopy has a prognostic impact. Semiquantitative counting of bacteria helps to differentiate between colonization and infection. As a less invasive procedure, a mini-BAL technique has been described. The diagnosis of ventilator-associated pneumonia is very difficult. It is made by the combination of clinical, radiological, and laboratory criteria (new infiltration, fever or hypothermia, leukocytosis or leukopenia, putrid tracheal secretions) and quantitative culture of tracheal aspirations or BAL. The cutoff of $\geq 10^5$ resp. $\geq 10^4$ CFU/mL is accepted as an indicator for ventilator-associated pneumonia.

Legionella infections can be detected either by direct immunofluorescence technique or by bacterial culture. Viral infections should be excluded using antibodies, viral cultures, and DNA-/RNA-probe analysis. To differentiate between acute, latent, or chronic persistent infection, the virus load must be measured by the number of genome equivalents, preferably in induced sputum or BAL. Electron microscopy can be used too.

Role of BAL in Research and Development of New Drugs

The discovery of new biomarkers and new signal pathways between cells and the application of proteomics, gene arrays, and metabolomics have contributed many important insights into the pathogenesis of respiratory tract diseases. BAL has been profiled as a pivotal method to obtaining alveolar space and airway specimens for research, and this could lead to more precise longitudinal monitoring of ILD in the future. For example, KL-6, a high molecular weight glycoprotein predominantly expressed on the surface of alveolar type II cells, is a promising biomarker in the field of ILD. Increased levels of KL-6 in BAL fluid and plasma correlate with the severity of alveolar inflammation and poor survival in acute respiratory distress syndrome. Increased levels of KL-6 in both BAL fluid and blood, with a strong correlation between BAL and blood, also reflect disease severity in patients with idiopathic pulmonary alveolar proteinosis.

BAL is suitable to study the cellular and biological changes induced by drugs. In this regard, BAL can be used for proof-of-concept studies in the clinical development of new drugs.

Conclusions

Since the early 1980s, BAL has been used to diagnose diffuse parenchymal lung disease. In addition, prognostic evaluation of ILD was made by BAL. It plays a crucial role in diagnosing rare disorders and in diagnosing or excluding

opportunistic infection. In the most centers, BAL is an important tool for the diagnostic approach and management of more common diseases as sarcoidosis, HP, or IPF. But this use of BAL is recently discussed controversially as there were important changes in disease classification. Most published studies fail to integrate BAL data with other clinical and radiological information. Further studies to assess the additional value of BAL are required.

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Radial Endobronchial Ultrasound

17

Felix J.F. Herth

Introduction

The endobronchial application of ultrasound has first been described in 1992. The following years, technical difficulties had to be solved, and a clear view on the indication and diagnostic properties of endobronchial ultrasound (EBUS) had to be developed. Many pathologies of the airways involve the bronchial wall and the parabronchial structures. Radiologic imaging has been proven to be unreliable in diagnostic evaluation of these structures, and bronchoscopy appears more useful for this application; however, the view of the endoscopist is limited to the lumen and the internal surface of the airways. Processes within the airway wall and outside the airways can only be assessed by indirect signs.

Since 1999, EBUS has been commercially available and gradually introduced in the bronchoscopic practice. This has broadened the view of the bronchoscopist and augmented the diagnostic possibilities for both bronchial and mediastinal abnormalities.

Some aspects have yet to be assessed when the technique is spread more widely. Considering the fact that it takes at least 50 sessions to acquire basic experience even in regular diagnostic bronchoscopy, it takes considerably more effort to gain expertise in this new diagnostic method, showing structures like the tracheal wall and imaging mediastinal structures from uncommon angles and points of view. The aim of this chapter is to describe the technique of performing radial EBUS and to discuss the results of published trial.

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The Development of Endobronchial Ultrasound

The imaging in ultrasound is different from the processes in X-ray imaging. It is the difference in resistance of different tissues to the ultrasound waves (impedance) which is more complex and only partly dependent on its water content. The different impedance of soft tissues has made ultrasound an indispensable diagnostic tool in medicine. Instruments that are used for gastrointestinal application could not be applied inside the airways because of their diameter. The main problem of application inside the airways is coupling of the ultrasonic probe to the tracheobronchial wall. For this purpose, lobar and smaller peripheral bronchi can be completely filled with water or saline solution. This is impossible in the central airways. In these with the naked probe, one gets only a very limited sectorial view (Fig. 17.1). For application inside the central airways, flexible catheters were developed with a balloon at the tip that allows circular contact for the ultrasound, providing a complete 360° high-resolution image of the parabronchial and paratracheal structures (Fig. 17.2). Once this balloon is filled with water, it completely fills the airway and provides a complete 360° view to the bronchial wall and the mediastinal structures. The water simultaneously serves as enhancing medium for the ultrasonic waves. Thus, under favorable conditions, even the depth of penetration for the 20-Mhz waves may be up to 5 cm. Radial EBUS is nowadays performed by inserting the ultrasound miniature probe through the instrument channel of a standard bronchoscope. The physician moves the probe forward and backward throughout the airway to obtain images of the surrounding tissue, so the physician can assess the internal structure of the lesion, determining its size, location, and depth of penetration.

Radial ultrasound allows for a 360° view of the exact location of a lesion in relation to the airway. This allows for

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more direct and accurate sampling, increasing the diagnostic yield of the procedure.

Miniprobes are delicate, fragile devices that must be handled with care. The transducer and the connecting driving wire are protected from friction inside the plastic sheath by a gel solution. The catheter might not be completely air sealed, and small air bubbles can collect in front of the transducer and interfere with the image. Therefore, the devices should be stored in a hanging position with the connector upward and the tip of the probe downward. If a bubble has collected at the tip of the catheter, it can be cleared by holding the probe approximately 40 cm proximally from the tip and rotating it like a lasso to drive the gel peripherally and the bubble proximally. After inserting the probe into the balloon catheter and connecting the proximal end to the connector with the driving unit, the catheter – including the balloon – should be filled completely with sterile water to clear the system from air and make slipping the O-ring over the notch easier. Olympus advice not to use saline solutions as the salt can crystallize on the probe and interfere with imaging. After filling, the O-ring can be slipped onto the tip of the probe with the fingertip or a special rubber device. This should be done gently without bending or kinking the tip. Then, the balloon is filled to expand. If some air bubbles remain, the balloon is kept with its tip pointing down, and the air is removed by suctioning the water from the balloon with the syringe. The syringe should always be held in an upright position so that the air collects above the fluid and is not flushed back into the catheter.

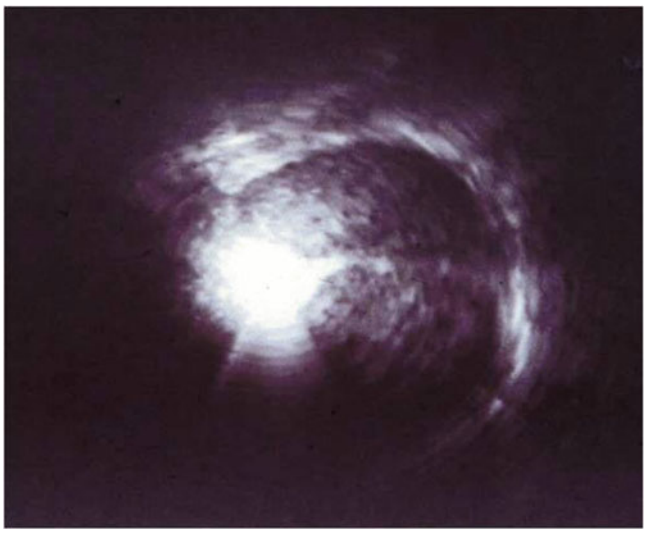

Fig. 17.1 View of the trachea with the unsheated probe. An image interpretation is not possible

After insertion via the biopsy channel of the flexible endoscope, precise placement of the probe inside the central airways is carried out under visual control. Once the transducer is positioned, the balloon is filled with water until firm contact with the wall is established. Adequate contact is confirmed by a complete circular image of the bronchial wall and the surrounding structures. The development of the image is similar to sunrise, when all the structures gradually become visible. After sufficient preoxygenation with the patient under local anesthesia, inflation of the balloon is possible in bilateral ventilated lungs up to the main bronchi and even inside the trachea. Complete obstruction of a remaining main bronchus after contralateral resection or occlusion of the trachea can be tolerated for up to 2 min with sufficient sedation.

The downside to using a radial probe is that the device must be removed from the bronchoscope channel before

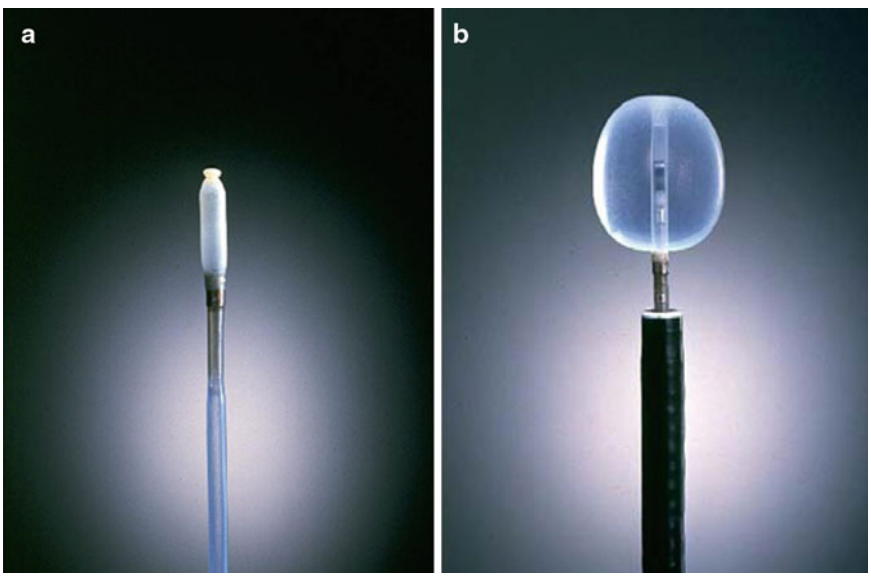

Fig. 17.2 The radial EBUS probe inside the water-fillable balloon sheath, filled and unfilled with sterile water

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 the specimen yield. After localization of the target, the probe is pulled out, and the needle is passed through the fiberscope in the retracted position. When the needle is in view, the needle is advanced from its sheath and inserted into the lesions through the tracheal or bronchial wall. After the needle is advanced into the tissue, suction is applied with a 20 ml syringe via a side port at the proximal end of the catheter. The technique is named EBUS-guided TBNA. The disadvantage of radial ultrasound highlights the advantages of the EBUS TBNA scope equipped with curvilinear ultrasound.

The new development is a dedicated bronchoscope with an integrated curvilinear electronic transducer at the tip. So a real-time needle puncture under endoscopic control is possible. The endoscope has a working channel of 2 mm. The ultrasonic frequency is 7.5 MHz with a penetration depth of 5 cm. The scanning direction is parallel to the longitudinal axis of the endoscope with a scanning angle of 50° which enables full ultrasonic monitoring of a needle when inserted via the biopsy channel during scanning but does not provide the necessary resolution for diagnostic imaging.

Sonographic Anatomy

The wall of the central airways shows a seven-layer structure (Fig. 17.3). The layers are representing the mucosa and submucosa, the three layers of the cartilage, and the adjacent external structures of lose and dense connective tissue, respectively (Fig. 17.4). Under low power magnification and in the periphery, only a three-layer structure is visible. Orientation by ultrasound within the mediastinum is difficult. Besides the complex mediastinal anatomy, this is due to motion artifacts by pulsation and respiration as well as the unusual planes of the ultrasonic images as dictated by the course of the airways. For orientation, therefore, the analysis of characteristic anatomical structures is more reliable than observation of the position of the ultrasound probe inside the airway (Fig. 17.5). Vessels can be identified by their pulsation. But even after application of echo contrast media, discrimination of venous and arterial vessels can be difficult due to the great number of variations (Fig. 17.6). However, as during the procedure pulse oxymetry is applied, arterial pulsations can be confirmed according to their synchrony with the acoustic signal. Lymph nodes and solid structures can be differentiated down to a size of few millimeters from the blood vessels by their higher echodensity.

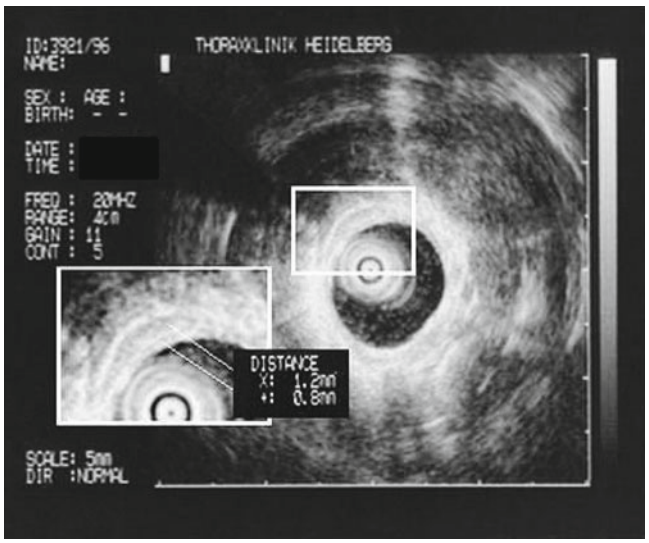

Fig. 17.3 The seven-layer structure of the trachea

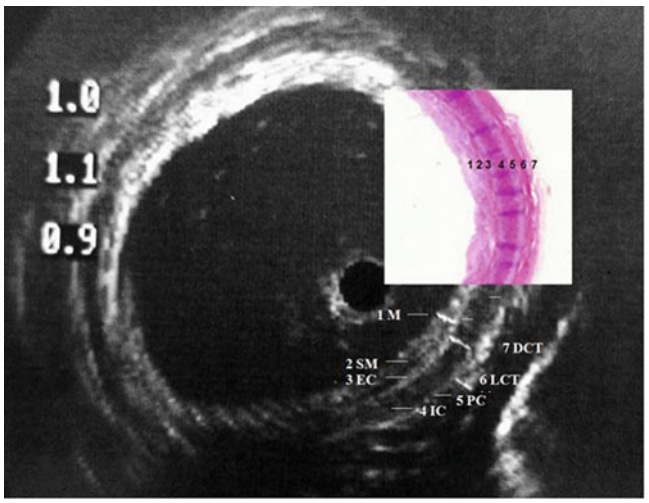

Fig. 17.4 The layer structure in detail. The three-layer structure of the cartilage with endochondrium (*EC*), perichondrium (*PC*), and spongiform internal structure (*IC*) is lined by mucosa (*MC*) and submucosa (*SM*) internally and by loose (*LCT*) and dense connective tissue on the outside (*DCT*). HE stain shows the corresponding structures

Indications and Results of Endobronchial Ultrasound-Miniprobe (MP) Application

For some indications, the superiority of ultrasound in comparison to conventional X-ray or CT imaging has been proven in prospective studies, and in many centers, EBUS is established as a routine procedure. According to the structures that can be analyzed, current indications comprise endoluminal, intramural, and parabronchial abnormalities, with respect to medical indications, early detection and tumor staging,

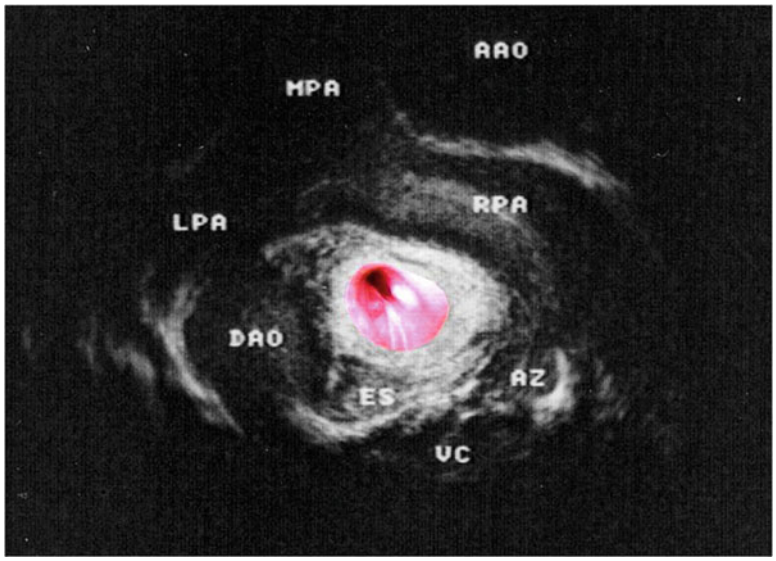

Fig. 17.5 US view of a compression of the airways due to the central vessels (*AAO* ascending aorta, *MPA* main pulmonary artery, *LPA* left pulmonary artery, *RPA* right pulmonary artery, *DAO* descending aorta, *ES* esophagus, *AZ* vena azygos, *VC* vertebral column)

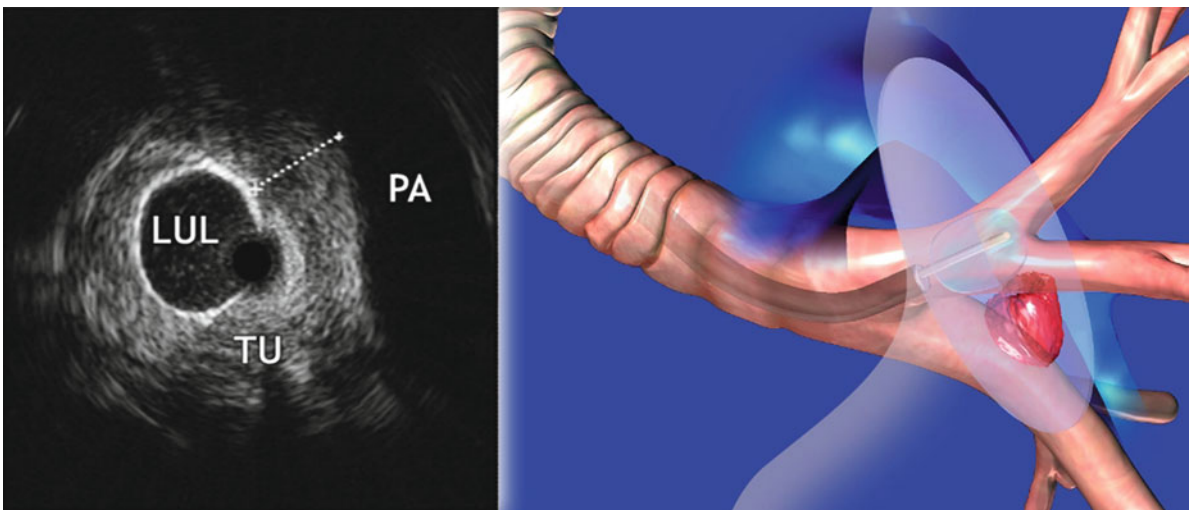

Fig. 17.6 The probe is placed in the upper lobe segment left (*LUL*), as seen in the animation. In the ultrasound image, the tumor (*TU*) is visible with close contact to the pulmonary artery (*PA*)

inflammatory destruction of the airways, mediastinal lesions, and malformations of mediastinal structures.

Tumor Staging

Early Cancer

In small radiologically invisible tumors, decision for local endoscopic therapeutic intervention is dependent on their intraluminal and intramural extent within the different layers of the wall. In contrast to CT imaging, endobronchial ultrasound can identify even very small tumors of few millimeters and differentiate them from benign lesions (Figs. 17.7–17.9). As demonstrated by Kurimoto et al., EBUS is a very reliable tool in analyzing the extent of these small lesions. When combining radial EBUS to autofluorescence in small autofluorescence (AF)-positive lesions that were negative in white light bronchoscopy (WLB), specificity (predicting malignancy) can be improved from 50% to 90%. Combination of EBUS with AF has been proven to be efficient in prospective studies and today has become the basis for decision making for curative endobronchial treatment of malignancies in some institutions. The most important study for this indication was published by Miazyu and colleagues. In 18 patients with clinically diagnosed early

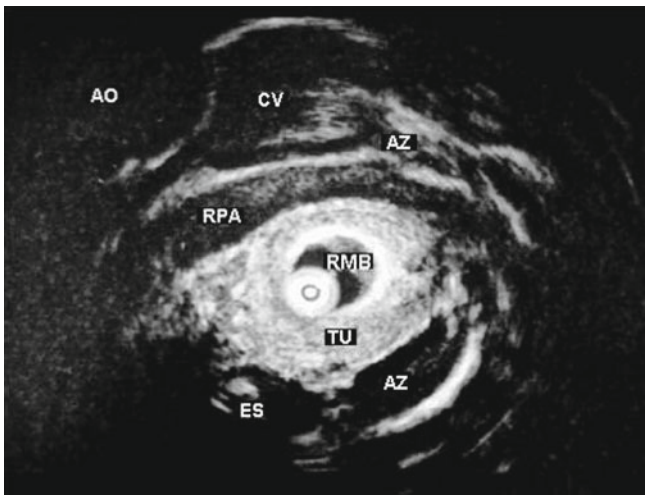

Fig. 17.7 US image of the right main bronchus (*RMB*). All surrounding structures are visible (*AO* aorta, *CV* vena cava, *AZ* vena azygos, *RPA* right pulmonary artery, *ES* esophagus). At a 7-o'clock position, a microinvasive tumor (*TU*) is visible

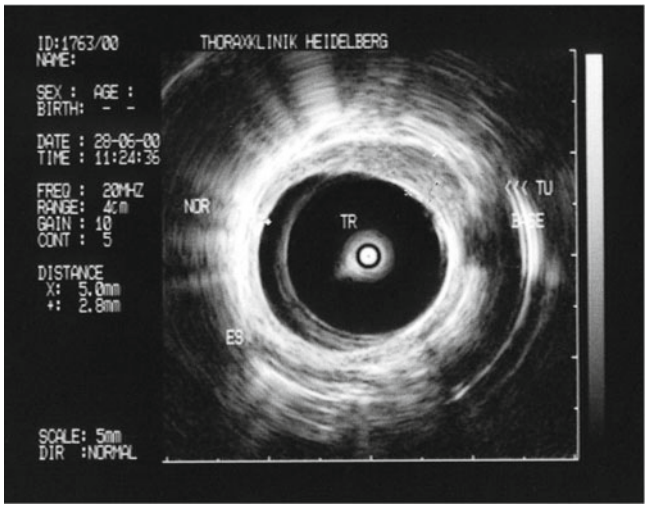

Fig. 17.8 A small tumor is seen at 2-o'clock in the trachea (*TR*) (*Nor* normal size of the wall, *ES* esophagus)

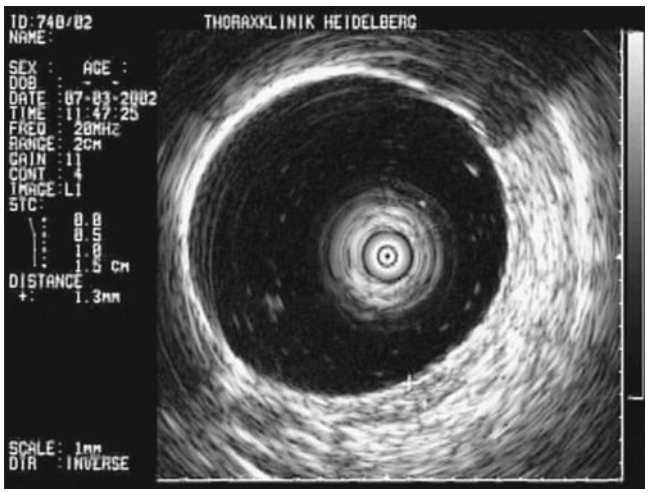

Fig. 17.9 Another example for a CIS, the enlarged cancer area is marked by the crosses

cancer of the airways, 9 were identified with EBUS with tumor limited to the bronchial wall. These patients were treated with photodynamic therapy with curative intent. All other patients had extracartilaginous tumor growth on EBUS imaging and therefore were treated with surgery, radiation, and/or chemotherapy. A 100% complete remission rate in the endoluminal-treated group was noted. In a mean follow-up time of 32 months, none of the patient developed a recurrence, as significant improvement over previously published results. Most authorities consider radial EBUS an integral component of the staging of primary airway cancer.

Advanced Cancer

In preoperative staging, EBUS allows detailed analysis of intraluminal, submucosal, and intramural tumor spread which can be essential for decision on resection margins. EBUS proved especially useful in the diagnosis of mediastinal tumor involvement of the great vessels such as aorta, vena cava, main pulmonary arteries, as well as of the esophageal wall which by conventional radiological means frequently is impossible (Fig. 17.10). In a trial, it was shown that differentiation of external tumor invasion from impression of the tracheobronchial wall by EBUS is highly reliable (94%) in contrast to CT imaging (51%). One hundred and four patients with central tumor were examined with EBUS and CT and classified into invasion or impression. All patients underwent surgery, and the findings were compared to the initial classification. The sensitivity (89–25%) and also the specificity (100–89%) proved the superiority of the ultrasound technique in the differentiation between airway infiltration and compression by tumor. Thus, many patients considered to be nonresectable by the radiologist due to supposed T4 tumors could be operated in a curative approach after radial EBUS examination.

Peripheral Lesions

For histological diagnosis of peripheral intrapulmonary lesions by bronchoscopic transbronchial biopsy, an instrumental approach under fluoroscopic or CT guidance is the standard procedure. This demands expensive X-ray equipment in the bronchoscopy suite or coordination with the

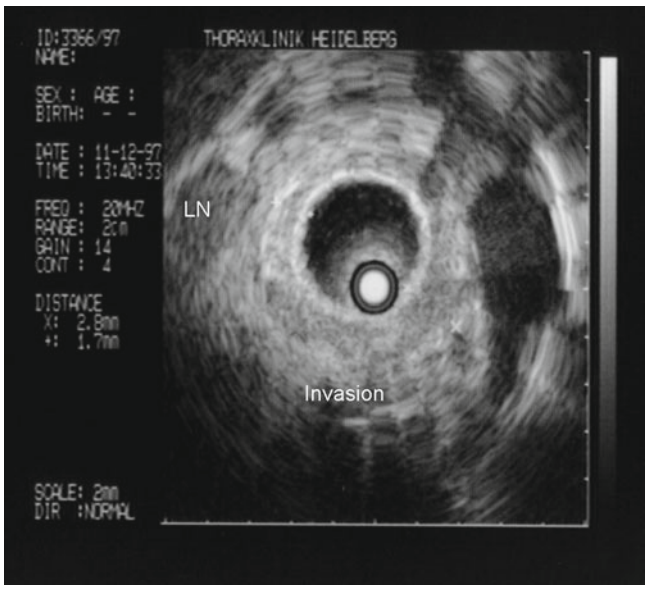

Fig. 17.10 Invasion of the left man bronchus is seen at the 6-o'clock position (*LN* lymph node)

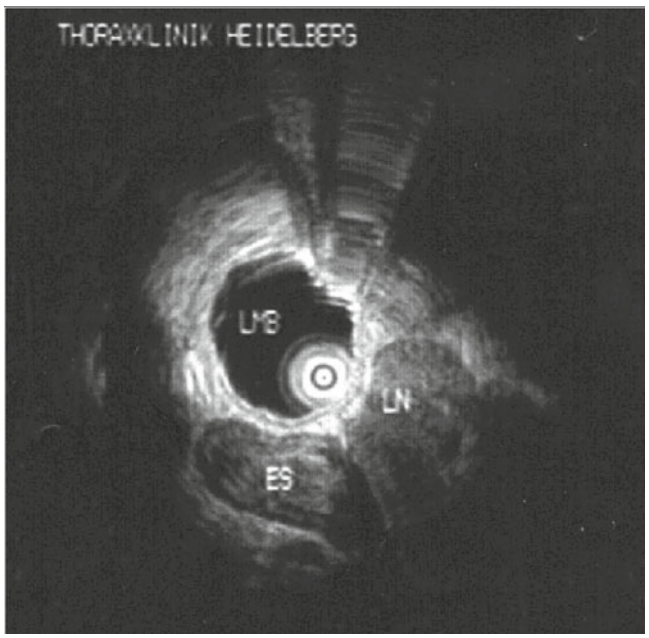

Fig. 17.11 Enlarged lymph node (*LN*) in position 10r seen in the 360° view (*LMB* left main bronchus, *ES* esophagus)

radiology department and causes exposure to radiation for patients and staff. EBUS-supported techniques are described in detail in other chapters.

Lymph Node Staging

Under favorable conditions, lymph nodes down to a size of 2–3 mm can be detected by EBUS, and the internal structure (sinuses and folliculi) as well as small lymph vessels can be analyzed. By adding endosonographic localization of lymph nodes, the results of transbronchial needle aspiration (TBNA) can be significantly improved to a yield of up to 85%. This is especially true for those positions in which reliable landmarks on the CT are missing, e.g., high and low paratracheal localization, such as LN station 2, 3, 4 in the IASLC scheme; the detection technique is helpful to increase the yield. On the other hand, EBUS guidance adds little if anything for enlarged lymph nodes in station 7 (Figs. 17.11 and 17.12).

Since the development of the dedicated EBUS TBNA scope, the use of miniprobes for guidance of TBNA is decreasing dramatically, even though the published results have shown good results.

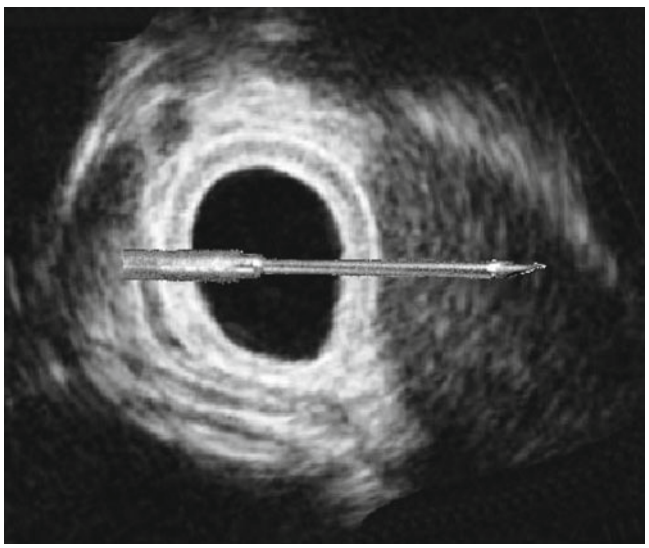

Fig. 17.12 Animation of an EBUS-guided TBNA. After detection of the lymph node, the probe has to be removed and replaced by the TBNA needle

Mediastinal Masses

Mediastinal masses can be analyzed and approached by EBUS for transtracheal and transbronchial needle biopsy if they are in close contact to the central airways or if a great vessel is providing an acoustic window. However, for investigation of retrosternal masses or of the dorsal mediastinum, penetration of EBUS is insufficient.

Great Vessels

Great vessels in the vicinity of the central airways are easily visualized due to their pulsation and low echo density. Stenosis of the central airways by compression due to vascular malformations is not uncommon in early childhood and can be evaluated in detail with radial EBUS, if needed. Diagnosis of thromboembolic complications of the venous

system is possible but generally an incidental finding. Rarely, bronchoscopists will be able to observe pulmonary embolism by endobronchial or endoesophageal ultrasound as suspicion for pulmonary embolism is no indication for an invasive procedure.

EBUS Guidance in Therapeutic Interventions for Advanced Malignancies

In decision for endobronchial therapy of advanced lung cancer, EBUS provides important data. In complete bronchial obstruction, the basis and surface of the tumor can be assessed. It can be assessed if the different layers of the bronchialwall are involved, how far the tumor is penetrating into the mediastinal structures, and whether the airways beyond the stenosis are patent. Also, patency of the adjacent pulmonary artery can be diagnosed, which is important to predict postinterventional perfusion of the dependent lung and prevent increase of dead space ventilation. EBUS is also useful for exploration of benign central airway stenosis to assess the extent and the cause of the disease and the relationship to vessels and other surrounding structures and to make the correct decision for therapy like mechanical dilatation, laser ablation or stent implantation, and endoscopic control of the results.

Conclusion

Endobronchial ultrasound has been widely available for more than 5 years. A growing body of good literature supports its significant role in airway assessment and procedure guidance. Its usefulness is especially well documented in lymph node staging via guided TBNA and in lending support for therapeutic decision making in regard to endoluminal or alternative treatment strategies for malignant airway abnormalities.

EBUS is a routine adjunct to endoscopy in many centers, and we expect its role to grow in the future.

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Linear Endobronchial Ultrasound

18

Kazuhiro Yasufuku

Introduction

Endobronchial ultrasound (EBUS) is a technology that allows the bronchoscopist to see beyond the airway. The linear endobronchial ultrasound also known as the convex probe endobronchial ultrasound (CP-EBUS) allows endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal and hilar lesions. Unlike conventional TBNA, the yield of EBUS-TBNA does not seem to depend on the expertise of the bronchoscopist due to the real-time procedure. EBUS-TBNA has changed the practice of bronchoscopic biopsy of the mediastinum, and in particular, the role of EBUS-TBNA for invasive mediastinal lymph node staging in lung cancer is becoming important.

EBUS-TBNA was initially developed for lymph node staging of lung cancer. However, from our experience, there are many other clinical applications. This chapter will cover and discuss in detail the actual procedure of EBUS-TBNA using the CP-EBUS as well as the clinical application of EBUS-TBNA.

Instrument

Convex Probe Endobronchial Ultrasound (CP-EBUS)

The currently available CP-EBUS is an ultrasound puncture bronchoscope with a 7.5-MHz convex transducer placed at the tip of a flexible bronchoscope (BF-UC180F-OL8, Olympus, Tokyo, Japan) (Fig. 18.1). The CP-EBUS is a linear curved array transducer that scans parallel to the insertion direction of the bronchoscope. Images can be obtained by directly contacting the probe (Fig. 18.1a) or by attaching a balloon on the tip and inflating with saline (Fig. 18.1b). The outer diameter of the insertion tube of the CP-EBUS is 6.2 mm and that of the tip is 6.9 mm. The angle of view is 80°, and the direction of view is 35° forward oblique. The unique optical system exploits both video and fiber-optic technologies. With the built-in CCD in the control section, it allows sharp images similar to those of regular video bronchoscopes. The inner diameter of the instrument channel is 2.2 mm. A dedicated 21- or 22-gauge needle is used to perform EBUS-TBNA (Fig. 18.1b).

Ultrasound Processor

The ultrasound image is processed by connecting the CP-EBUS to either the dedicated ultrasound scanner (EU-C60, Olympus, Tokyo, Japan), the universal endoscopic ultrasound scanner with capabilities of radial probe EBUS imaging (EU-ME1, Olympus, Tokyo, Japan), or the Aloka Prosound Alpha5 (Aloka) for excellent image quality (Fig. 18.2). The EU-ME1 is equipped with the power Doppler mode as well as the color Doppler mode (Fig. 18.3). The ultrasound images can be captured, and the size of lesions can be measured in two dimensions by the placement of cursors. The area and the circumference enclosed by caliper tracking can be measured as well.

Dedicated TBNA Needle

Two types of dedicated needles are available for EBUS-TBNA. The 21-gauge (NA-201SX-4021) or the 22-gauge needle (NA-201SX-4022) passed through the 2.2-mm instrument channel allows real-time EBUS-TBNA (Fig. 18.2d). This needle has various adjuster knobs which work as a safety device to prevent damage of the channel. The maximum extruding stroke is 40 mm, and to prevent excessive protrusion, a safety mechanism stops the needle at the stroke

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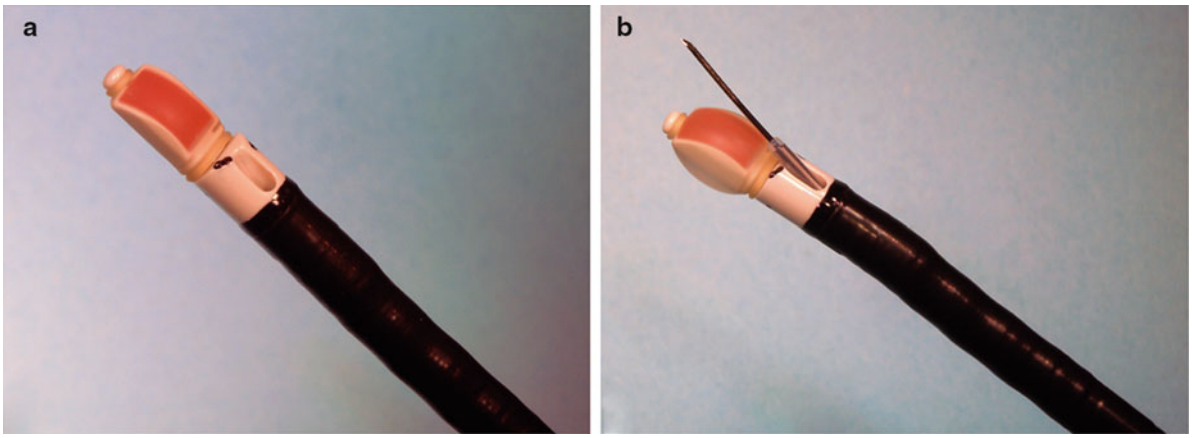

Fig. 18.1 Tip of the new convex probe endobronchial ultrasound (CP-EBUS, BF-UC160F-OL8, Olympus, Tokyo, Japan). The outer diameter of the insertion tube of the flexible bronchoscope is 6.2 mm. CP-EBUS has a linear curved array ultrasonic transducer of 7.5 MHz (**a**). The balloon attached to the tip of the bronchoscope is inflated with normal saline, and a dedicated TBNA needle is inserted through the working channel (**b**)

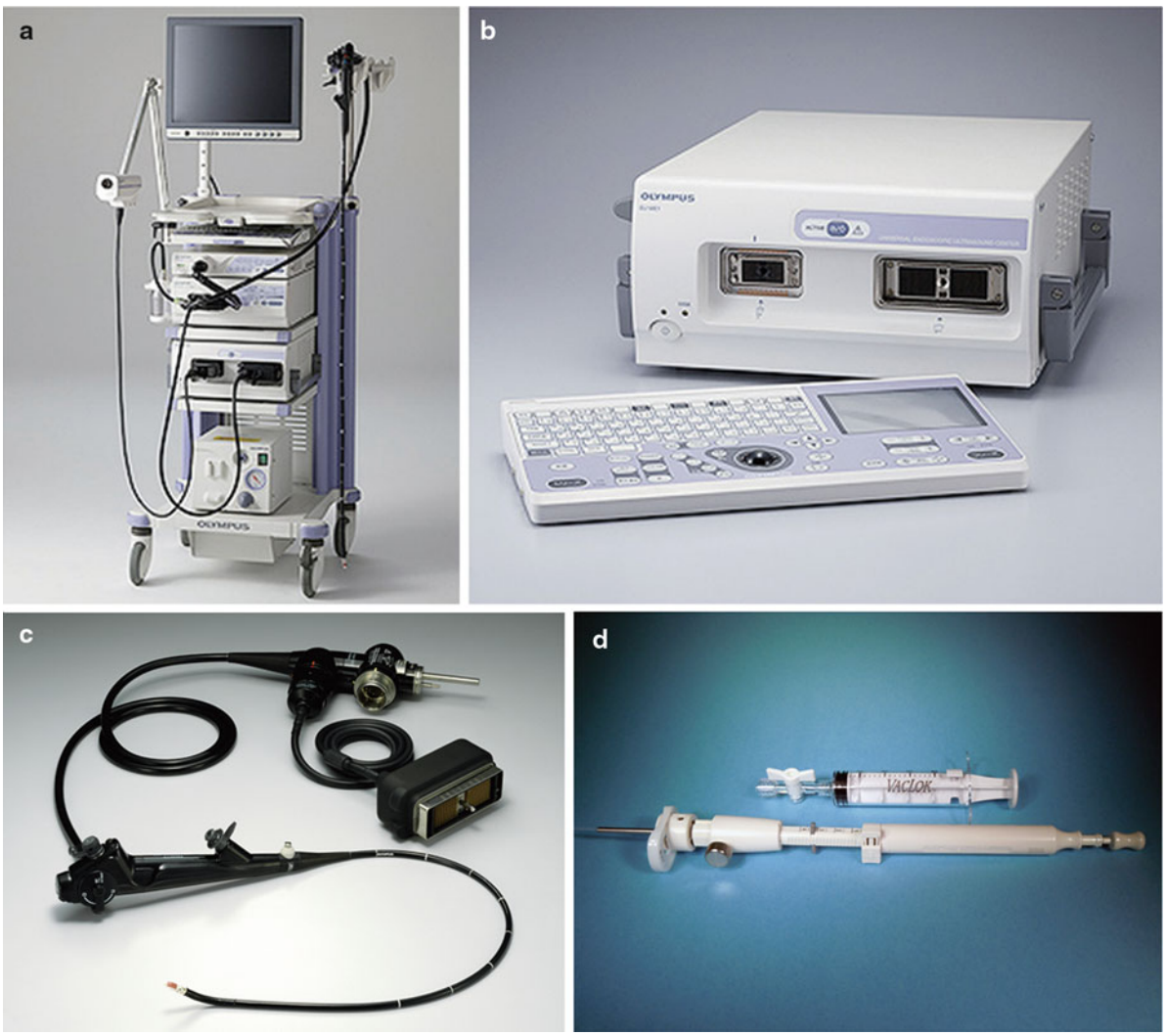

Fig. 18.2 The endobronchial ultrasound system. The tower includes the universal endoscopic ultrasound scanner with capabilities of radial probe EBUS imaging as well as the convex probe endobronchial ultrasound (EU-ME1, Olympus, Tokyo, Japan) (**a**, **b**). The convex probe endobronchial ultrasound (CP-EBUS, BF-UC180F-OL8, Olympus, Tokyo, Japan) (**c**) is used with the dedicated 22- or 21-gauge needle (NA-201SX-4022/NA-201SX-4021, Olympus, Tokyo, Japan) and the Vaclok syringe used to create negative pressure (**d**)

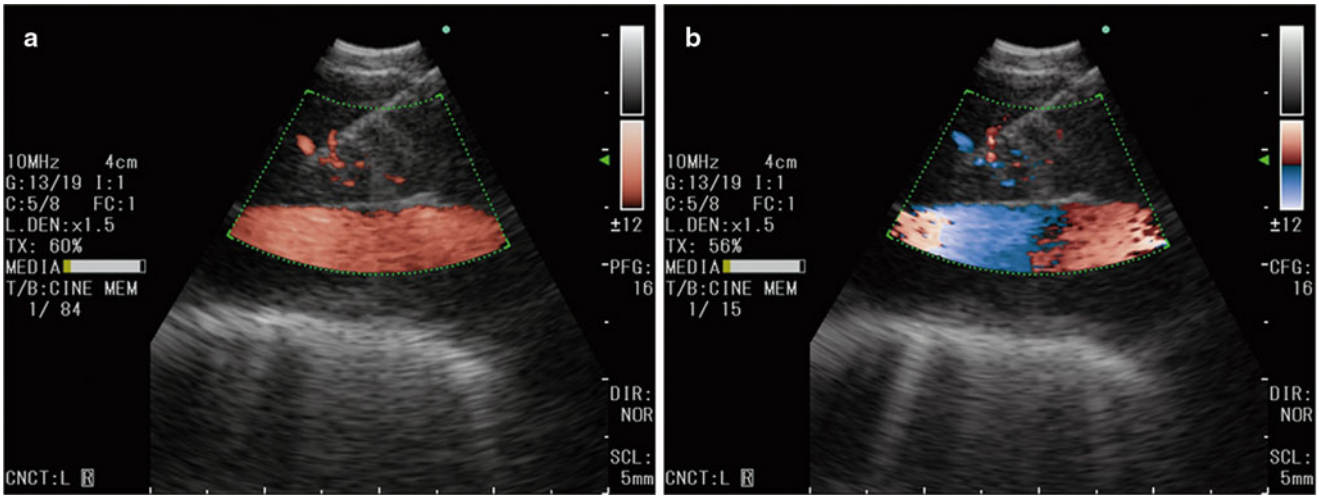

Fig. 18.3 The ultrasound processor is also equipped with the power Doppler mode (**a**) as well as color Doppler mode (**b**)

of 20 mm. The needle is also equipped with an internal sheath which is withdrawn after passing the bronchial wall, avoiding contamination during TBNA. This internal sheath is also used to clear out the tip of the needle after passing the bronchial wall. The exit of the needle is at 20° with respect to the outer covering of the insertion tube. The needle can be visualized through the optics and on the ultrasound image.

Procedural Technique

Anesthesia

EBUS-TBNA can be performed on an outpatient basis under conscious sedation. The bronchoscope is usually inserted orally, since the ultrasound probe on the tip will limit nasal insertion. Some investigators prefer the use of the endotracheal tube or rigid bronchoscopy under general anesthesia. An endotracheal tube larger or equal to size 8 is required due to the size of the EBUS-TBNA scope. Cough reflex is minimal under general anesthesia which may be an advantage during the procedure. However, operators should be careful not to put excessive pressure with the probe on to the airway. The disadvantage of the endotracheal tube is that it causes the bronchoscope to lie in the central position within the airway which creates difficulty to bring its tip in close proximity to the trachea or bronchus. The use of the laryngeal mask airway has been shown to be useful during EBUS-TBNA.

Insertion to Visualization of Lymph Nodes

Two separate monitors should be used during EBUS-TBNA: one for the endoscopic image and one for the ultrasound image (Fig. 18.4). Since the linear curved array transducer is on the tip of the flexible bronchoscope, the optic located proximal to the ultrasound probe is set at a 35-degree forward oblique angle. Therefore, in order to obtain a straight view, the tip of the bronchoscope needs to be slightly flexed down. The bronchoscopist also needs to be aware that the 7.5-MHz ultrasound probe attached on the tip of the bronchoscope is not visible without the inflation of the balloon. Careful attention should be made to advance the scope atraumatically.

After achieving local anesthesia and conscious sedation, the CP-EBUS is inserted orally and passed through the vocal cords by visualizing the anterior angle of the glottis (Fig. 18.5a). Once the bronchoscope is introduced into the airway until the desired position is reached for EBUS imaging (Fig. 18.5b), the balloon is inflated with normal saline to achieve a maximum contact with the tissue of interest. The tip of the CP-EBUS is flexed and gently pressed onto the airway. Ultrasonically visible vascular landmarks are used to identify the specific lymph node stations according to the International Lymph Node Map by the International Association for the Study of Lung Cancer. The Doppler mode is used to confirm and identify surrounding vessels as well as the blood flow within lymph nodes. There is a standard EBUS classification system of sonographic features of lymph nodes on EBUS. One can predict malignant versus benign during lymph node staging with EBUS-TBNA. Lymph nodes larger than 1 cm in short axis, round shaped, distinct margins, heterogeneous echogenicity, with the presence of coagulation necrosis sign and without the presence of central hilar structures are suspicious for malignancy and need to be biopsied (Fig. 18.6).

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA)

After identifying the lesion of interest, the bronchoscopic image of the airway is simultaneously visualized to localize the insertion point of the needle. Once the point of entry is

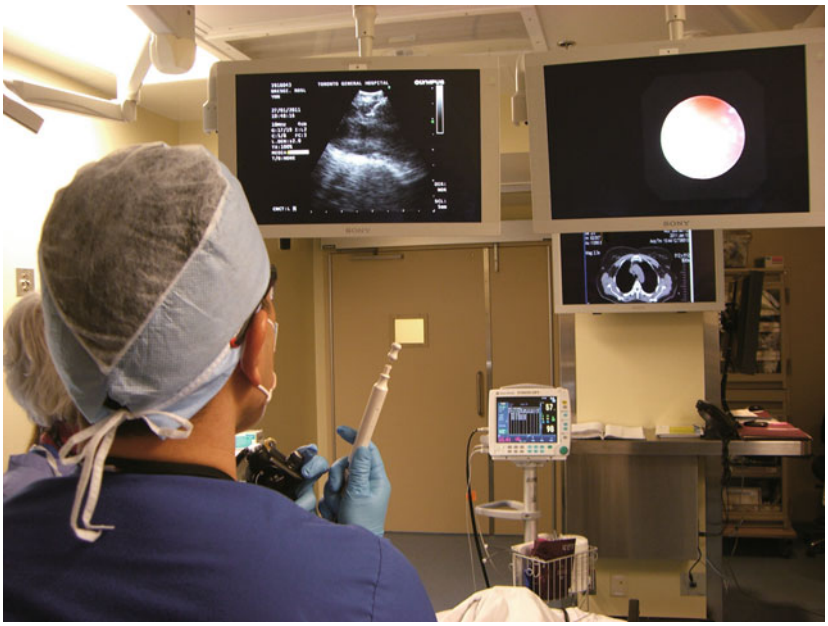

Fig. 18.4 Bronchoscopists performing endobronchial ultrasound-guided transbronchial needle aspiration under local anesthesia. A two-screen display is preferable for endobronchial images as well as ultrasound images during the procedure

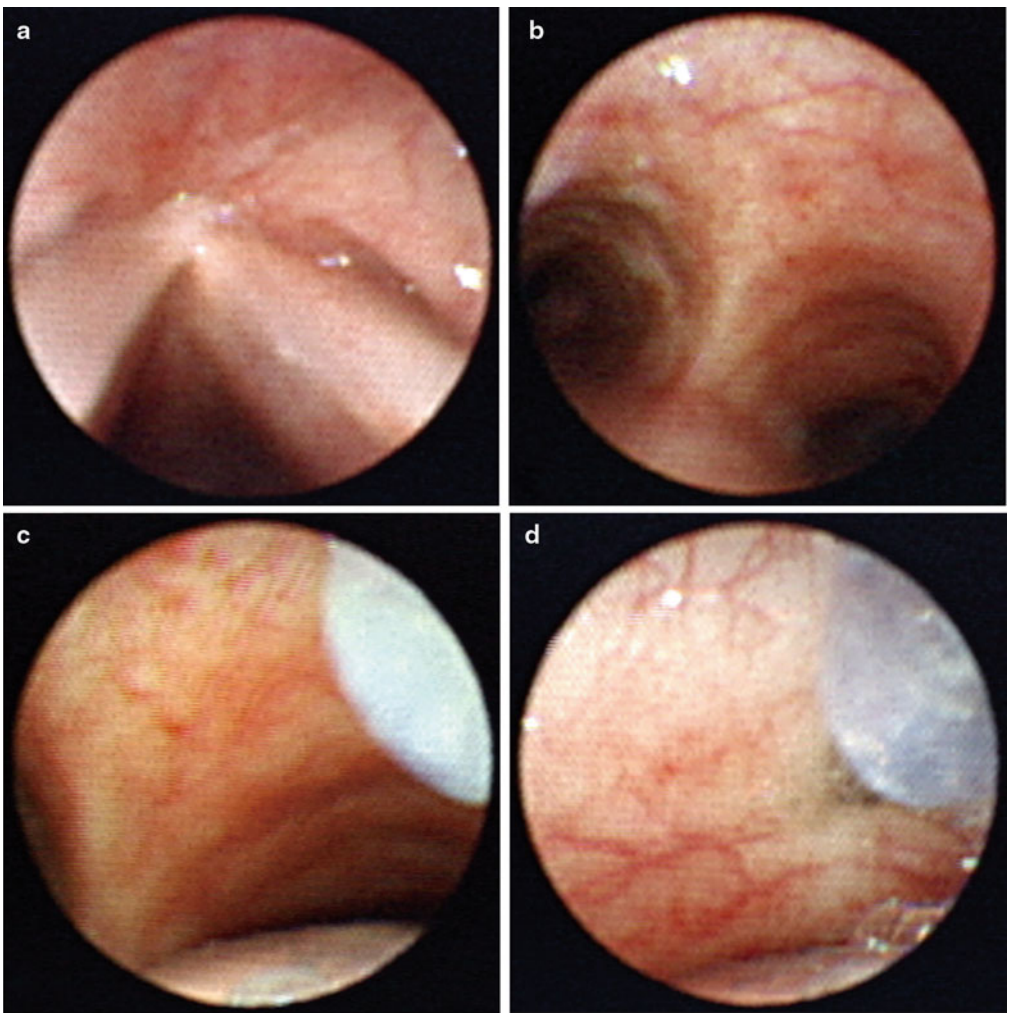

Fig. 18.5 Endobronchial images of the EBUS-TBNA procedure. The bronchoscope is passed through the vocal cords by visualizing the anterior angle of the glottis (**a**). In order to obtain a straight view, the bronchoscope needs to be slightly flexed down (**b**). The balloon is inflated with normal saline for maximum contact, and the tip is gently pressed onto the airway (**c**). The needle is passed through the intercartilage space (**d**)

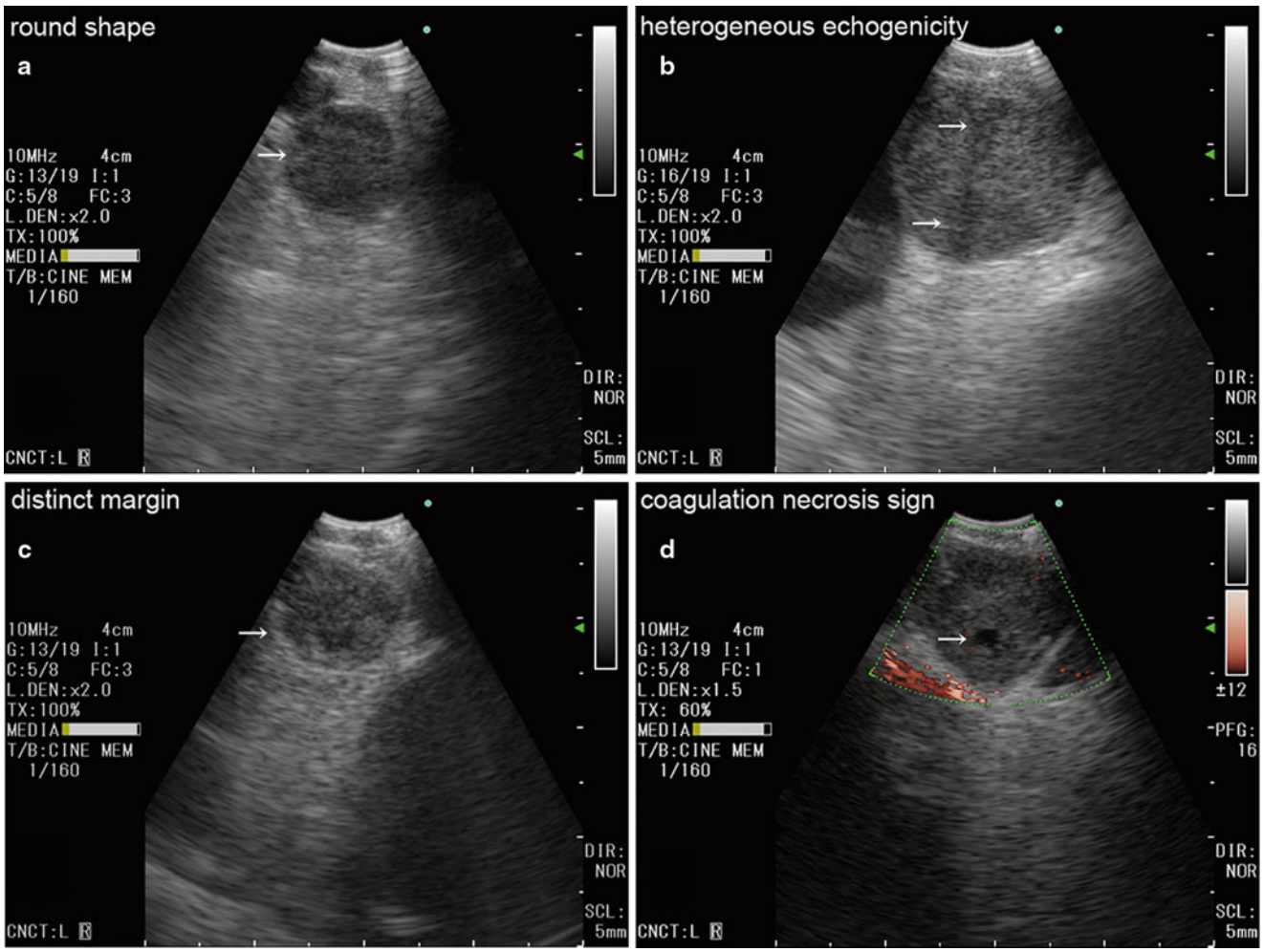

Fig. 18.6 Sonographic features of lymph nodes during endobronchial ultrasound. Lymph nodes with the following characters: round shape (**a**), heterogeneous echogenicity (**b**), distinct margin (**c**), and presence of coagulation necrosis sign (**d**) are independent predictive factors for lymph node metastasis and should be biopsied. *White arrows* represent each sonographic characteristics

decided using small landmarks on the airway, the dedicated TBNA needle is fastened on to the working channel of the bronchoscope. The manipulation of the needle is a very important element of performing EBUS-TBNA and is shown in Fig. 18.7. The sheath adjuster knob is loosened, and the length of the sheath is adjusted so that the sheath can be visualized on endoscopic image (Fig. 18.5c). The tip of the bronchoscope is flexed up for contact, and the lymph node is visualized again on ultrasound image. After the needle adjuster knob is loosened, the needle can be passed through the airway into the lymph node. The cartilaginous ring should be avoided during penetration (Fig. 18.5d). Once the needle is confirmed inside of the lymph node, the internal stylet is used to clear out the internal lumen, which may become clogged with bronchial membrane. The internal sheath is then removed, and negative pressure is applied with the Vaclok syringe. In case of a hyper vascular lymph node, negative pressure may cause bloody samples; thus, EBUS-TBNA can be done without suction. The needle is moved back and forth inside the lymph node to obtain samples. Finally, the needle is retrieved inside of the outer sheath, and entire needle is removed from the bronchoscope.

It is extremely important to process the specimen obtained by EBUS-TBNA in a proper way to achieve maximum results. Although the EBUS-TBNA procedure can be performed successfully by following the steps explained in this chapter, handling of the specimen may differ between centers, and this would depend on the preference of the cytopathologist and thus should follow your institutional standards. The internal stylet is usually used to push out samples. With the presence of a cytopathologist, the first few drops are placed on the slide glass, and smears are made for rapid on-site cytological evaluation using Diff-Quik staining (Fig. 18.8). The rest of the specimen is placed in a 50-ml conical filled with normal saline for cellblock preparation. The remaining specimen within the needle is also washed in this conical.

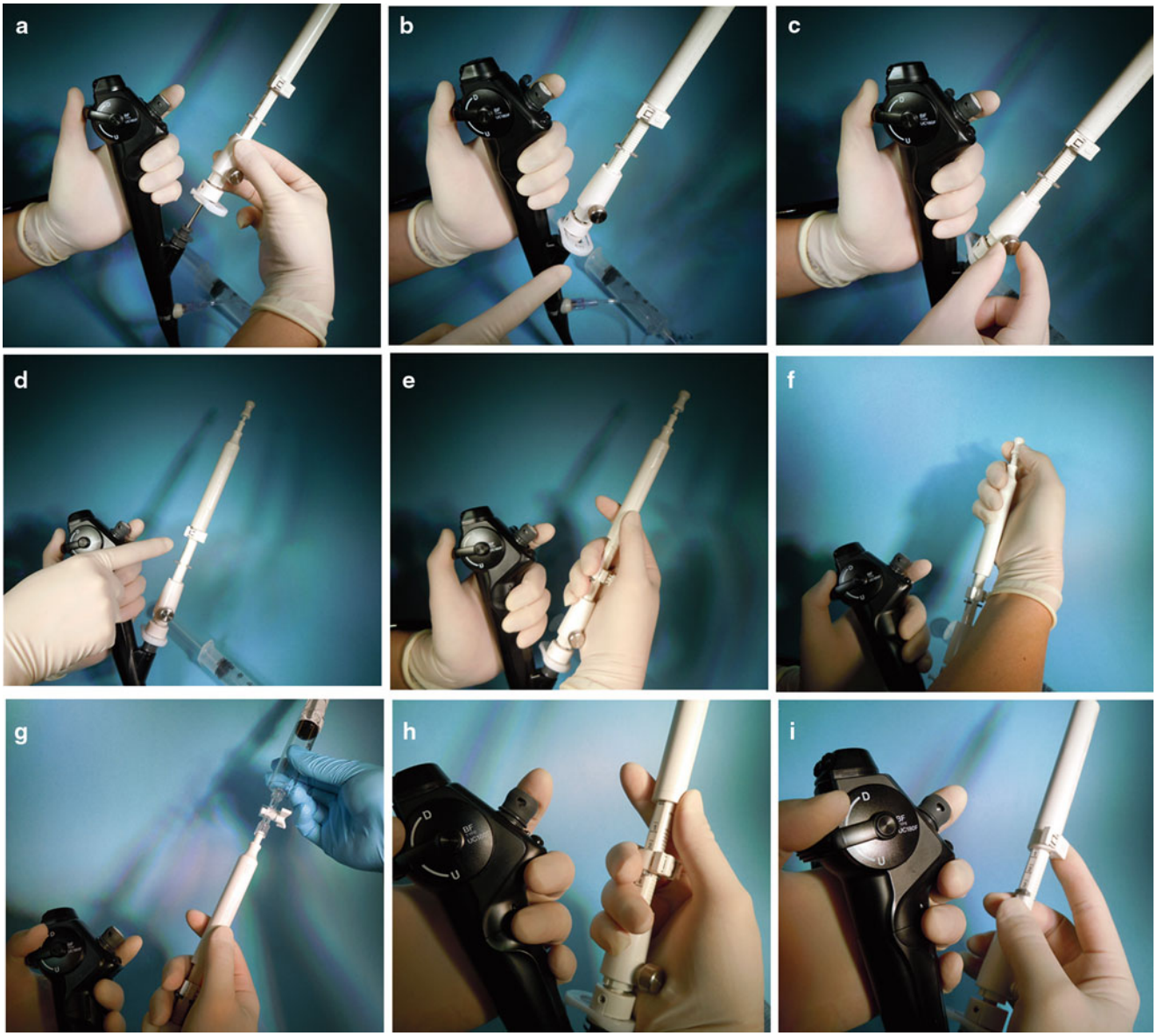

Fig. 18.7 Manipulation of the dedicated needle. The assistant should assist the operator so that the needle does not kink during this process (**a**). The needle is fastened on to the working channel (**b**). The sheath adjuster is loosened and the length adjusted (**c**). The needle adjuster is unlocked (**d**). EBUS-TBNA is performed (**e**). After the initial puncture, the internal stylet is used to clear out the internal lumen (**f**). Negative pressure is applied with the Vaclok syringe (**g**). Pull the needle back into the outer sheath until you hear the click on the needle (**h**). Lock the needle and pull the outer sheath back into the channel of the bronchoscope (**i**)

Systematic Assessment of Mediastinal and Hilar Lymph Nodes

Prior to EBUS-TBNA, all of the mediastinal and hilar lymph nodes should be assessed, characterized, and documented in a systematic way. Lymph nodes should be identified according to the International Lymph Node Map by the International Association for the Study of Lung Cancer (Fig. 18.9). The vascular anatomy is used for identification of the lymph nodes. The authors prefer to start the lymph node assessment from the hilum, working up into the mediastinum and ending in the contralateral hilum. To avoid contamination and upstaging, EBUS-TBNA should be performed from the N3 nodes, followed by N2 nodes and N1 nodes.

Representative lymph node stations, bronchoscopic landmarks for optimal ultrasound visualization, and ultrasound images of lymph nodes and surrounding vessels are explained in details below.

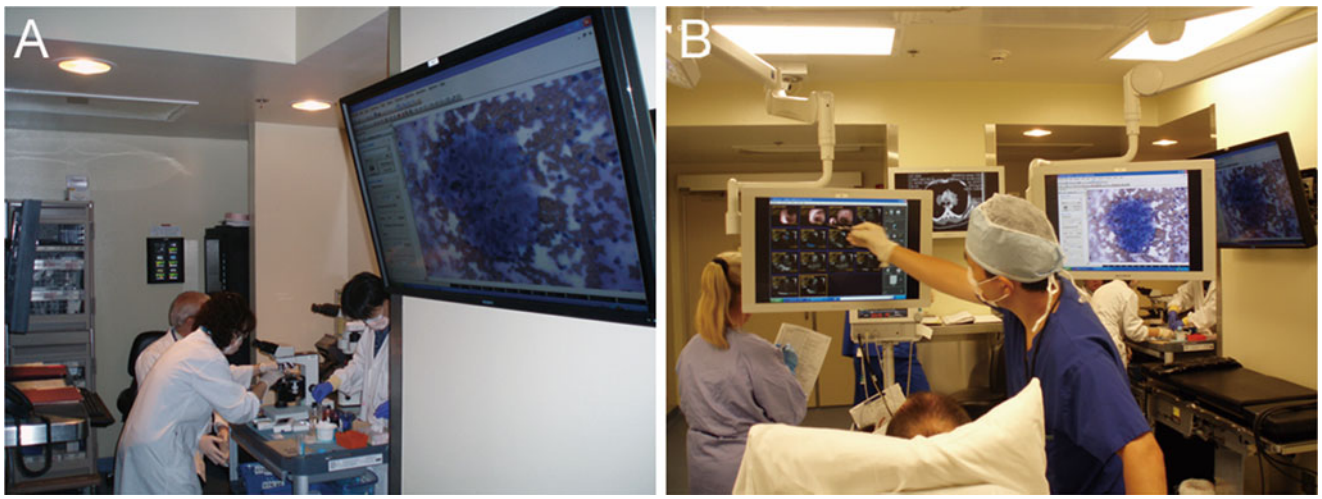

Fig. 18.8 Rapid on-site cytological evaluation of aspirates. Results of rapid on-site cytological evaluation are projected on to a large display in the Interventional Thoracic Surgery Suite (**a**). The results of the procedure can be explained to the patient immediately after the completion of the procedure (**b**)

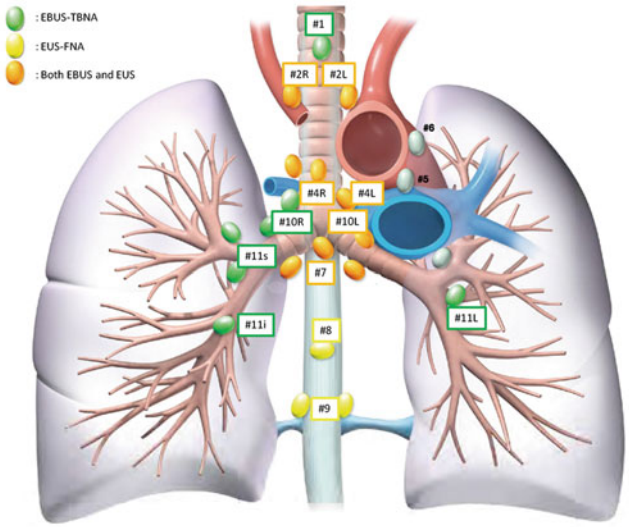

Fig. 18.9 Regional lymph node map for lung cancer staging. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration. EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

Station #12R

The bronchoscope is advanced into the right lower lobe bronchus. The tip of the CP-EBUS is flexed up against the lower lobe bronchus just proximal to where the basal bronchus branches. Station #12R can be visualized adjacent to the interlobar pulmonary artery.

Station #11R

Straighten and withdraw the bronchoscope to the intermediate bronchus. Turn to the 2-o'clock position and flex the tip just distal to the entrance of the right upper lobe bronchus. Station #11R can be visualized with the interlobar pulmonary artery running distal to the lymph node.

Station #10R

Withdraw the bronchoscope to the right main bronchus. Turn the tip to the 3-o'clock position and flex the tip to visualize station #10R. Lymph nodes identified distal to the azygos vein is station #10R.

Station #7

Station #7 can be visualized from either the right or the left main bronchus. On the right side, turn to the 12-o'clock position and flex the tip against the right main bronchus to

visualize the right main pulmonary artery. After confirmation with the Doppler mode, turn the tip counterclockwise to the 9-o'clock position to visualize station #7.

Station #4R

Withdraw the bronchoscope to the trachea looking straight toward the main carina. Turn to the 2-o'clock position and flex the tip just proximal to the main carina. Visualize the SVC and the azygos vein branching from the SVC. Station #4R is located proximal to the azygos vein close to the SVC.

Station #2R

While visualizing the SVC on the ultrasound image, withdraw the bronchoscope maintaining contact with the trachea at the 2- to 3-o'clock position. The SVC will bifurcate to the left and right brachiocephalic veins. Any lymph node distal to the bifurcation along the right side of the trachea is station #2R.

Station #1

Withdraw the bronchoscope further to visualize the right brachiocephalic artery. Any lymph node above the bifurcation of the right and left brachiocephalic vein along the trachea is station #1.

Station #2 L

Once again, visualize the right brachiocephalic artery on the ultrasound image. The tip is located at the 2- to 3-o'clock position in the upper trachea. Maintaining contact with the trachea and following the brachiocephalic artery on ultrasound image, push the bronchoscope back distally into the trachea. By following the brachiocephalic artery, the tip will consequently be turned counterclockwise. At the midtrachea level 12-o'clock position, the brachiocephalic artery will run into the aortic arch. The aortic arch is the vascular landmark for differentiating station #2 and #4. Lymph node present on the left side of the trachea above the aortic arch is station #2 L.

Station #4 L

Facing the main carina, turn the bronchoscope to the 10-o'clock position and flex the tip just proximal to the main carina and scan the area for station #4 L. The aortic arch can be followed to the aortopulmonary window. The aortic arch is proximal and the left main pulmonary artery is distal.

Station #10 L

Advance the bronchoscope into the left main bronchus at the 10-o'clock position by following the left pulmonary artery on ultrasound image. This is the area of station #10 L.

Station #11 L

Further advancing the bronchoscope into the left lower lobe bronchus, flex the tip at the 2-o'clock position in the carina of the upper and lower lobe bronchus. Station #11 L is visualized adjacent to the interlobar pulmonary artery.

Station #12 L

By advancing the bronchoscope further into the basal segmental bronchus or the upper lobar bronchus, station #12 L can be visualized. However, due to the angle of the left upper lobe bronchus, oftentimes it is difficult to identify these nodes.

Indication

Indications for EBUS-TBNA are the assessment of mediastinal and hilar lymph nodes, diagnosis of lung tumors, and diagnosis of mediastinal tumors. All of the mediastinal lymph nodes except for the subaortic and paraesophageal lymph nodes (stations 5, 6, 8, and 9) are assessable by EBUS-TBNA through the airway. Lymph node stations 8 and 9 can be visualized if the CP-EBUS is passed through the esophagus. Due to the size of the linear probe, lobar lymph nodes around the upper lobe cannot be visualized.

Lymph Node Staging by EBUS-TBNA

EBUS-TBNA has significantly changed the minimally invasive approach to mediastinal and hilar staging in patients with NSCLC. Evidence-based clinical practice guidelines on mediastinal staging now suggest invasive techniques including EBUS-TBNA for the confirmation of patients with clinical N2 or N3 disease. The current literature, including systematic reviews and meta-analyses, has demonstrated a major impact of EBUS-TBNA on management of patients with lung cancer.

The first prospective study of EBUS-TBNA for lung cancer staging in 105 patients showed a high sensitivity of 95%, negative predictive value of 90%, and diagnostic accuracy of 96%. EBUS-TBNA also avoided 50 more invasive sampling procedures (29 mediastinoscopies, 8 thoracotomies, 4 thora-

coscopies, and 9 CT-guided FNA). The largest multicenter prospective study in lung cancer staging covered 502 patients with mediastinal and hilar adenopathy. A total of 572 lymph nodes were punctured using the CP-EBUS resulting in successful diagnoses in 535 lymph nodes. The sensitivity and negative predictive value of EBUS-TBNA for detecting malignancy were 94% and 11%, respectively. Recent studies have also shown the role of EBUS-TBNA in patients without mediastinal lymph node enlargement.

Although PET scan has a relatively high negative predictive value, for patients with discrete mediastinal lymph node enlargement, staging by CT or PET alone is not sufficiently accurate. PET-positive lesions require tissue confirmation to prove that the lesions are truly malignant. Several studies have looked at the role of EBUS-TBNA in combination with PET scan for mediastinal staging in NSCLC. A comparison study of EBUS-TBNA, CT, and PET for lymph node staging of lung cancer showed a higher yield in favor of EBUS-TBNA (diagnostic accuracy: CT 60.8%, PET 72.5%, EBUS 98.0%). Additional studies have shown high sensitivities as well as high negative predictive values of EBUS-TBNA in PET hot spots.

Neoadjuvant therapy (chemotherapy, radiotherapy) prior to surgical resection is an option for selected stage IIIA NSCLC. However, restaging of the mediastinum can be challenging due to technical difficulties of remediastinoscopy and therefore has not been commonly performed. In contrast, EBUS-TBNA allows multiple, repeat biopsy in a minimally invasive way which prompted a study in 124 consecutive patients with tissue-proven IIIA-N2 disease that were treated with induction chemotherapy. EBUS-TBNA for restaging showed a sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 76%, 100%, 100%, 20%, and 77%, respectively. The performance of EBUS-TBNA for restaging was comparable to that of mediastinoscopy.

A combined EBUS-TBNA and transesophageal endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) offers a wider coverage of the mediastinum in a minimally invasive way. In general, EBUS-TBNA is limited to sampling mediastinal and hilar lymph nodes adjacent to the airway. The subaortic (levels 5, 6) and paraesophageal lymph nodes (levels 8, 9) are not accessible by CP-EBUS. EBUS offers better access to the paratracheal and hilar lymph node stations, while EUS can easily sample paraesophageal lymph nodes in the inferior mediastinum. The left lower paratracheal lymph node (4L) can be biopsied by both techniques, but this can be a challenging lymph node station to sample by EBUS due to the angle. EUS-FNA may be technically easier to sample lymph nodes station 4L with the flexibility of the esophagus. Although the two techniques are complementary to each other, EUS-FNA is predominantly performed by gastroenterologists and in some healthcare systems; it can be difficult for pulmonologist to gain accreditation in EUS-FNA. To solve this problem, the CP-EBUS has been used through the esophagus as an alternative to EUS-FNA with great success.

Systematic reviews have confirmed equivalent sensitivity for EBUS-TBNA to mediastinoscopy for staging NSCLC. However, the high prevalence of mediastinal disease in EBUS-TBNA compared to mediastinoscopy studies limits the comparison and extrapolation of the results. The negative predictive value of mediastinoscopy is still higher in mediastinoscopy compared to EBUS-TBNA; thus, negative EBUS-TBNA findings in the setting of high pretest probability of malignancy should be validated with a mediastinoscopy. On the other hand, a negative EBUS-TBNA in the setting of low probability of malignancy may be helpful. There have been very few comparative studies on EBUS-TBNA and mediastinoscopy. The limited studies show that EBUS-TBNA may reduce the number of mediastinoscopy needed for the staging of the mediastinum in NSCLC. However, due to the possibility of micrometastases, it is not clear that EBUS-TBNA will completely replace mediastinoscopy for mediastinal staging.

Most of centers have adopted to perform EBUS-TBNA under local anesthesia, and EBUS-TBNA has been shown to be a safe procedure. The systematic reviews report only one incidence of morbidity in a patient with pneumothorax following the procedure (0.07% morbidity) with only minor issues of agitation, cough, and presence of blood at the puncture site reported. The cost-effectiveness for mediastinal staging also seems to be in favor of EBUS-TBNA over mediastinoscopy.

Based on the current evidence, EBUS-TBNA presents a minimally invasive procedure as an alternative to mediastinoscopy for mediastinal staging of NSCLC with discrete N2 or N3 lymph node enlargement, provided negative results are confirmed by surgical staging. EBUS-TBNA has replaced mediastinoscopy in many patients with diffuse mediastinal adenopathy, where a simple tissue diagnosis is required to determine treatment. EBUS-TBNA offers the advantage of obtaining a diagnosis as well as lymph node staging simultaneously in an outpatient setting. Initial mediastinal lymph node staging by EBUS-TBNA will allow mediastinoscopy to be reserved for restaging after induction treatment.

EBUS-TBNA for Mediastinal Lymphadenopathy of Unknown Origin

Although introduced as an invasive staging tool for mediastinal and hilar lymph nodes in lung cancer, EBUS-TBNA can be used for the diagnosis of other mediastinal lymphadenopathy of unknown origin as well as other mediastinal processes. The study for the diagnosis of mediastinal masses of

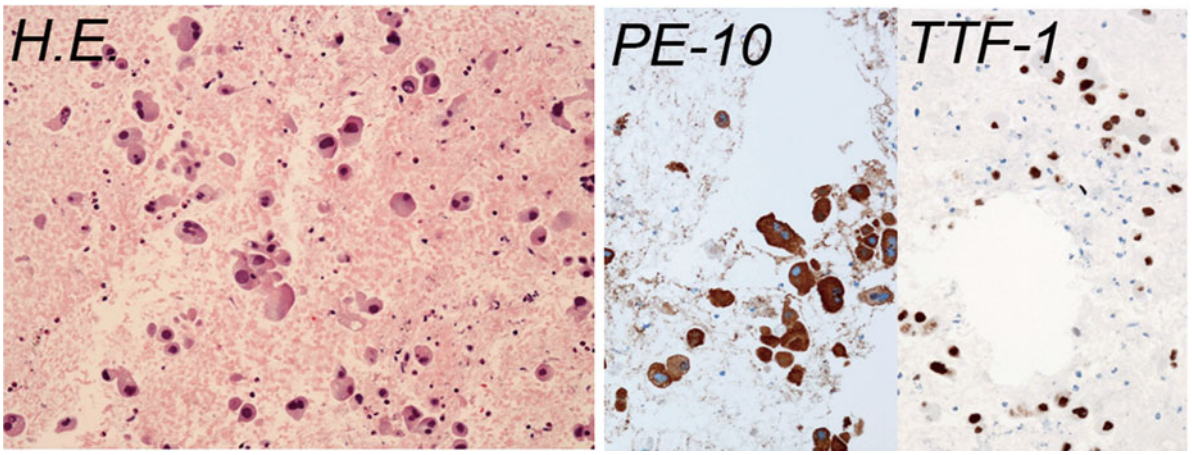

Fig. 18.10 Cytopathological findings of mediastinal lymph node biopsied by EBUS-TBNA. Hematoxylin and eosin (*HE*) staining shows adenocarcinoma cells. Immunohistochemical analysis shows tumor cells positive for surfactant apoprotein A (*PE-10*) and thyroid transcription factor-1 (*TTF-1*) (*brown* stain)

unknown etiology using EBUS-TBNA showed that EBUS-TBNA was diagnostic in 93.6% for all disease categories (malignant 87.5%, benign 96.0%). Since EBUS-TBNA can directly sample lymph nodes in the mediastinum or the hilum, it has been shown to be useful in the diagnosis of sarcoidosis. There is also evidence for the utility of EBUS-TBNA for the diagnosis of lymphoma. Other than lung cancer, EBUS-TBNA can be used for the detection of mediastinal lymph node involvement in metastatic lung tumors. Immunohistochemistry is especially helpful to correlate the histology of the metastatic lymph nodes to the primary tumor (Fig. 18.10).

Molecular Analysis Using EBUS-TBNA Samples

The availability of multiple histological cores from the present 22-gauge needle has raised the possibility of molecular diagnosis from EBUS-TBNA-obtained specimens. In addition, a larger, dedicated 21-gauge needle is now commercially available and has contributed to providing a larger tissue for various analyses. In lung cancer patients with N2 or N3 disease proven by EBUS-TBNA, DNA extracted from paraffin-embedded samples has been shown to be feasible for the detection of EGFR mutations. Methylation analysis as well as extraction of RNA from EBUS-TBNA samples has been demonstrated, although not standardized. RNA from metastatic lymph nodes can be used for aberrant fusion gene detection (EML4-ALK fusion gene). The ability to perform biological analysis using nonsurgical biopsy samples using EBUS-TBNA will become very important for the future of lung cancer treatment.

Complications

With the increasing number of EBUS-TBNA being performed, one may raise the question of the safety of the procedure. Potential complications related to EBUS-TBNA are similar to those of conventional TBNA, including bleeding from major vessels, pneumothorax, bronchospasm, and laryngospasm. The systematic reviews report only one incidence of morbidity in a patient with pneumothorax after the procedure (0.07% morbidity) with only minor issues of agitation, cough, and presence of blood at the puncture site being reported. There are case reports of infection after EBUS-TBNA, which may suggest prophylactic use of antibiotics in selected cases. From our experience in over 2,000 cases, we have not yet encountered complications related to EBUS-TBNA. The only complication or problem related to EBUS-TBNA has been the damage to CP-EBUS. EBUS-TBNA is indeed a very safe modality with a high yield.

It will be extremely difficult to prevent wear and tear of the bronchoscope, but damage to the bronchoscope based on human error should be and can be avoided. Every bronchoscopist and the team assisting the procedure should fully understand the instrument, including the dedicated needle, before performing EBUS-TBNA.

Conclusion

The convex probe EBUS enables a safe and precise evaluation of the mediastinum as well as the hilum in a minimally invasive way. The reach of EBUS-TBNA is similar to a cervical mediastinoscopy but also extends to the hilar lymph

nodes. From the current evidence, EBUS-TBNA presents a minimally invasive procedure as an alternative to mediastinoscopy for mediastinal staging of NSCLC with discrete N2 or N3 lymph node enlargement, provided negative results are confirmed by surgical staging. EBUS-TBNA also has the utility in the diagnosis of sarcoidosis and lymphoma. From our current experience, EBUS-TBNA should be used as the first test for patients with undiagnosed mediastinal lymphadenopathy if available. Complications are rare with either EBUS modality and are usually related to the transbronchial biopsy procedure.

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Esophageal Ultrasound

19

Jouke T. Annema

Introduction

Esophageal ultrasound-guided fine-needle aspiration (EUS-FNA) enables visualization and real-time ultrasound-guided biopsy of lesions located adjacent to the intestinal tract. Initially, EUS was developed for gastroenterologists for the staging of esophageal cancer and the analysis of pancreatic lesions. To date, a large body of evidence exists demonstrating that EUS-FNA is a valuable technique for the diagnosis and staging of lung cancer. By combining esophageal with endobronchial ultrasound (EBUS), a minimally invasive evaluation of virtually all mediastinal nodes can be achieved. Implementation of endosonography results in improved nodal staging, a markedly reduced need for mediastinoscopy, and less futile thoracotomies as compared to surgical staging alone. Additionally, EUS is a useful technique for the analysis of posterior mediastinal masses and for the staging of the mediastinum in patients with (previous) extrathoracic cancer. For nonmalignant diseases, EUS-FNA is a safe and accurate technique to demonstrate granulomas in patients suspected of sarcoidosis and tuberculosis.

Esophageal Ultrasound Procedure

As tissue verification of mediastinal nodes is almost always indicated in pulmonary medicine, only linear – and not radial – endosonography equipment is used. These echo-endoscopes have a convex linear array ultrasound transducer incorporated at the distal tip of the endoscope (Fig. 19.1). A frequency of 7.5 MHz is most commonly used, and the ultrasound beam ranges between 120° and 180° along the axis of the scope. An oblique optical viewer is available which may be used during the introduction of the endoscope in the esophagus. Traditionally, EUS scopes from gastroenterology are used, but recently it has been demonstrated that an esophageal ultrasound investigation can also be performed using smaller endobronchial (EBUS) scopes. Whether esophageal nodal assessment with an EBUS scope can replace a conventional EUS equipment has to be evaluated.

Esophageal ultrasound is performed in fasting patients lying in a left lateral position under conscious sedation using a low dose of midazolam. A thorough knowledge of mediastinal anatomy is a prerequisite for an EUS investigation as only ultrasound images are available for orientation. A standardized EUS evaluation in patients with (suspected) lung cancer starts by identifying the left adrenal gland from the stomach. Subsequently, the endoscope is retracted stepwise while making circular movements in order to visualize all mediastinal nodes that can be detected from the esophagus. The following anatomical landmarks are used for orientation: celiac axis, liver, vena cava, right atrium, left atrium, pulmonary artery, and aorta. Nodes that are observed by EUS are described in relation to those vascular structures and given the appropriate number according to the TNM classification system. Lesions adjacent to the esophagus can be aspirated under real-time ultrasound control. Nodes with a round shape, a short axis >10 mm, sharp demarcation, and a hypoechoic echo texture are more likely to be malignant involved. Elastography, a novel technique measuring tissue stiffness (Fig. 19.2), might be helpful in selecting the optimal target area to obtain tissue.

In the absence of on-site cytology, four needle passes will result in an optimal yield and minimize false-negative results. The standard needle size is 22 gauge, but also 19 gauge and Tru-Cut needles are available. Suction is mostly applied, but the necessity of it has been questioned in recent studies. From the aspirates, tissue blocks can be made on which immunohistochemistry staining and molecular analysis can be performed. On average, an evaluation of the left adrenal gland and all mediastinal nodes that can be detected by EUS including

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Fig. 19.1 Linear EUS-FNA scope (Hitachi-Pentax FG 34 UX) with a convex linear array ultrasound transducer, sheet, and 22-gauge needle

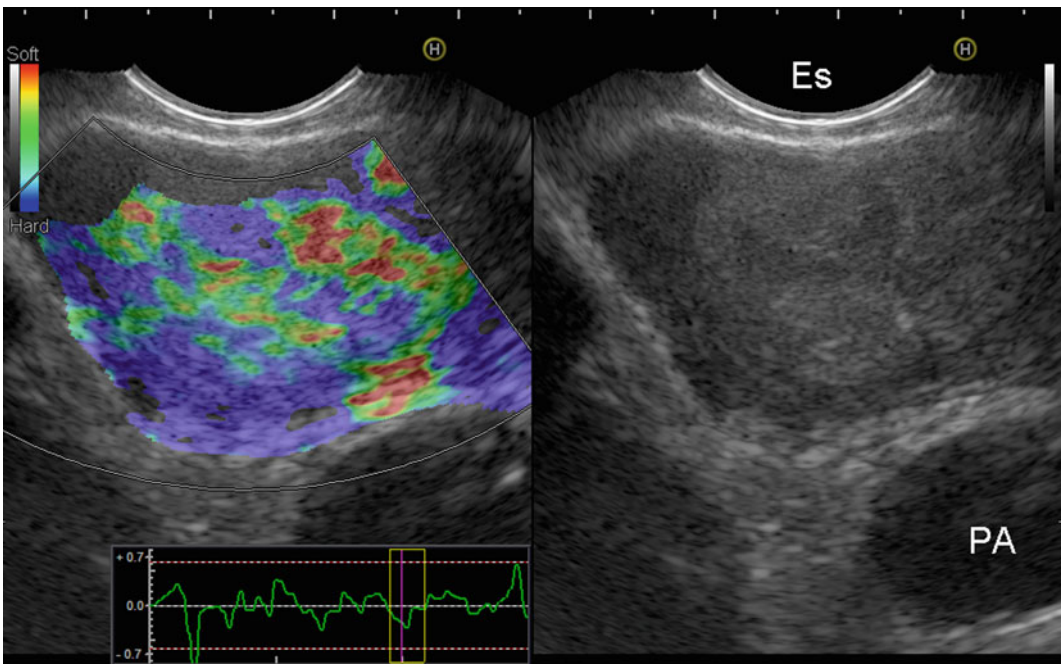

Fig. 19.2 EUS image of a subcarinal mass (station 7) in the *left-panel* "elastography" is used. *Blue* colors correspond with areas of increased tissue stiffness in comparison to the *red* and *green* areas. *PA* pulmonary artery, *ES* esophagus

aspirations takes around 20 min. Importantly, EUS has a very low complication rate and is well tolerated by patients. This is especially of importance in patients with severe COPD and an advantage to an endobronchial approach.

Mediastinal EUS can be taught to chest physicians without prior gastroscopy or ultrasound experience applying a limited but dedicated implementation strategy. Learning EUS anatomy is the most time consuming; the actual aspiration of nodes is relatively straightforward and easier in comparison to a transbronchial route due to the absence of the cartilage rings. Training tools to assess competency in EUS are under evaluation.

Table 19.1 Indications for esophageal ultrasound (EUS) in chest diseases

Suspected lung cancer
– Enlarged or PET-positive mediastinal lymph nodes within reach[a]
– Primary lung tumor located adjacent to the esophagus
Staging of non-small cell lung cancer
– Mediastinal staging (regardless of nodal size at CT)
– Mediastinal involvement at FDG-PET[a]
– Mediastinal restaging after induction chemotherapy[a]
– Suspected mediastinal tumor invasion (T4)
– Suspected left adrenal metastasis
Analysis of mediastinal masses
– Solitary mediastinal masses
– Suspected mediastinal metastases in patients with (previous) extrathoracic cancer[a]
Suspected sarcoidosis

[a] Nodes with reach of EUS (lower mediastinum, left paratracheal region, aortopulmonary window)

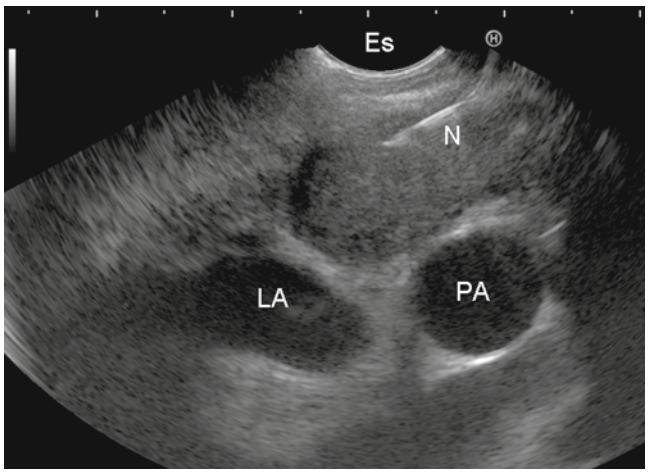

Fig. 19.3 EUS-guided fine-needle aspiration (*N*) of a subcarinal node (station 7) located between esophagus (*ES*), left atrium (*LA*), and pulmonary artery (*PA*)

Lung Cancer

Diagnosing and staging of lung cancer is the most common indication for EUS-FNA in pulmonary medicine (Table 19.1). By providing tissue proof of a mediastinal nodal metastasis, a diagnosis and locoregional staging can be achieved with a single minimally invasive test. Besides nodal staging, EUS-FNA can be used to obtain tissue of centrally located intrapulmonary tumors and the left adrenal gland.

Nodal Staging

EUS-FNA provides access to nodes located in lower mediastinum (subcarinal region station 7) (Fig. 19.3), lower paraesophageal area (station 8), and pulmonary ligament (station 9). Nodes located paratracheally to the left (station 4L) (Fig. 19.4), in the aortopulmonary window (station 5) (Fig. 19.5), and the para-aortal region (Fig. 19.6) can be detected by esophageal ultrasound. Aspiration of small left paratracheal nodes is often easier from the esophagus (Fig. 19.4B) – in comparison to an EBUS approach – due to absence of cartilage rings and cough reflexes. The aortopulmonary nodes can only be aspirated safely in selected cases due to the intervening pulmonary artery (Fig. 19.5B). The para-aortal nodes (Fig. 19.6) can be approached transaortally. Nodes paratracheally to the right (stations 2R and 4R) can regularly only be detected by EUS when enlarged. The esophagus is located in a left dorsal position in relation to the trachea, so air prevents visualization of these mediastinal areas. For enlarged nodes (short axis > 10 mm), EUS has a sensitivity of 90 %. EUS can also be used for a reevaluation of the mediastinum after induction chemotherapy.

Tumor Staging

Centrally located intrapulmonary tumors located adjacent or near the esophagus (Fig. 19.7) or aorta (Fig. 19.8) can be detected and aspirated by EUS. For those patients with a centrally located lung tumor without endobronchial abnormalities, EUS is often an accurate and safe test to obtain a tissue diagnosis. EUS provides an attractive alternative to CT-guided biopsy; the latter is often not possible due to the close proximity of the pulmonary vasculature and increased risk of pneumothorax. In addition to assessing a tissue diagnosis, EUS can often make an assessment regarding the presence (Fig. 19.9) or absence (Fig. 19.8B) of mediastinal/vascular tumor invasion (T4 tumor, stage IIIB).

Left Adrenal Gland

The left adrenal gland is a predilection site of metastatic spread for bronchogenic carcinoma. From the stomach, the left adrenal gland can be detected and typically presents with a seagull shape (Fig. 19.10). Loss of the "seagull shape" (Fig. 19.11), increased size, and FDG-PET uptake are predictors for malignant involvement.

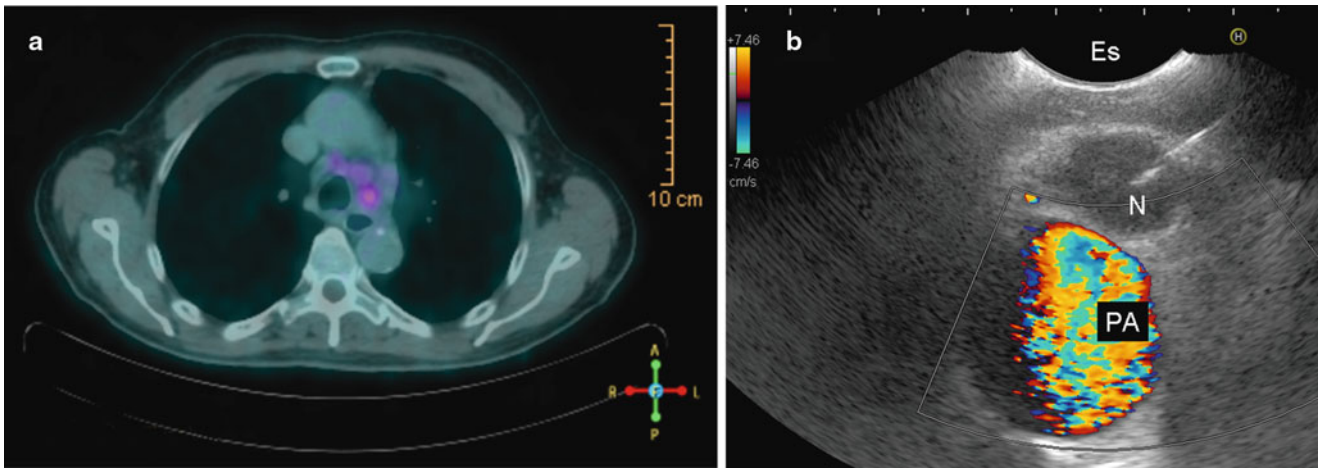

Fig. 19.4 (**a**) Integrated positron emission and computed tomography (PET-CT) scan with FDG uptake in a lower left paratracheal node (station 4L). (**b**) Corresponding EUS-guided FNA (*N* needle) of the lower left paratracheal lymph nodes located between the esophagus (*Es*) and pulmonary artery (*PA*)

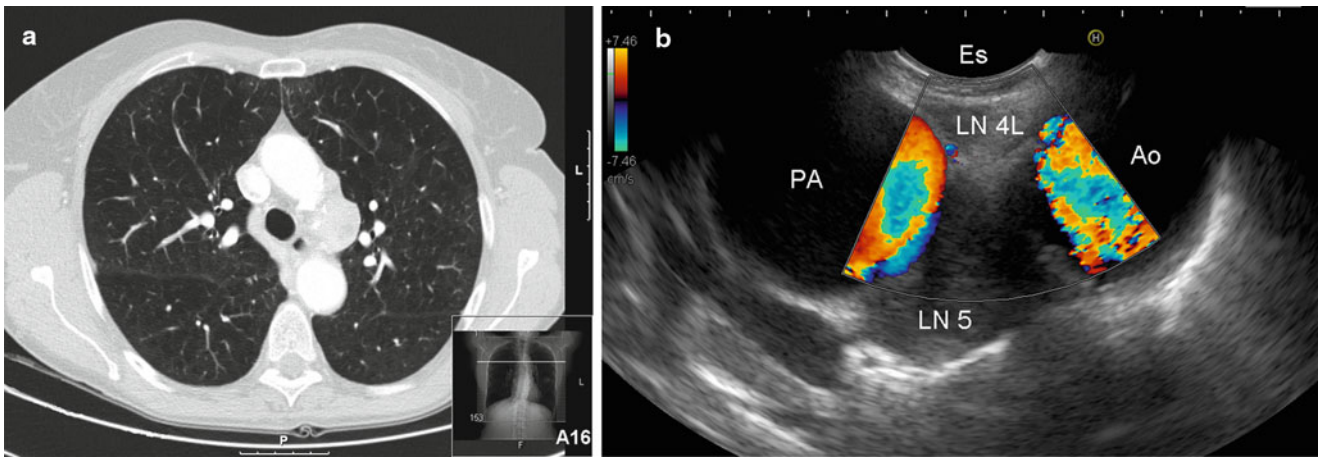

Fig. 19.5 (**a**) Computed tomography of the chest showing enlarged mediastinal nodes in the aortopulmonary window (station 5). (**b**) Corresponding EUS image, showing the left lower paratracheal node (station 4L) and the nodes in the aortopulmonary window. *AO* aorta, *PA* pulmonary artery, *ES* lumen of the esophagus

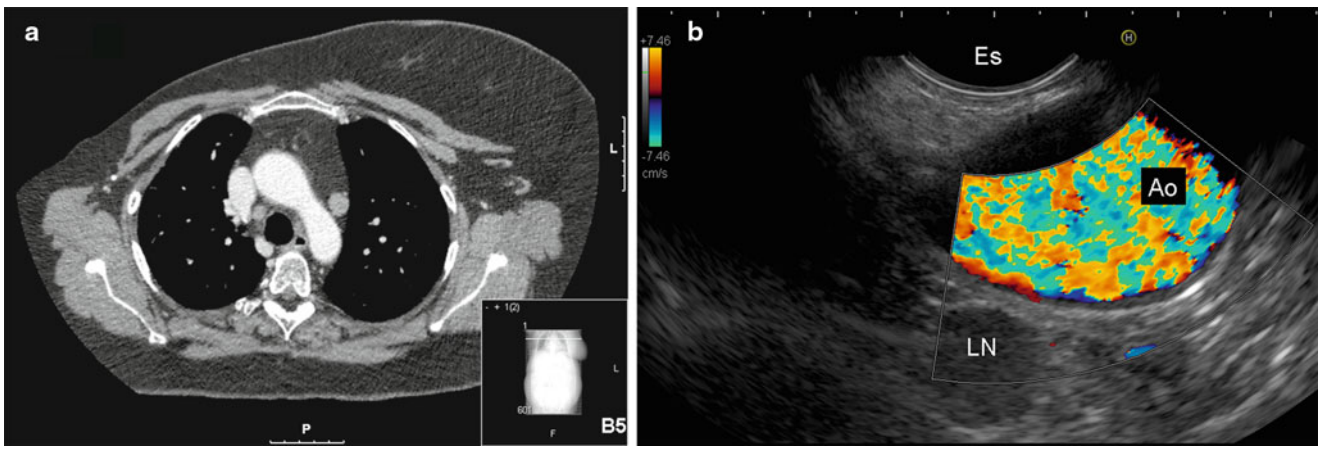

Fig. 19.6 (**a**) Computed tomography of the chest demonstrating a para-aortal node (station 6). (**b**) Corresponding EUS image, the para-aortal node (*LN*) is seen transaortally (*AO*). *ES* esophagus

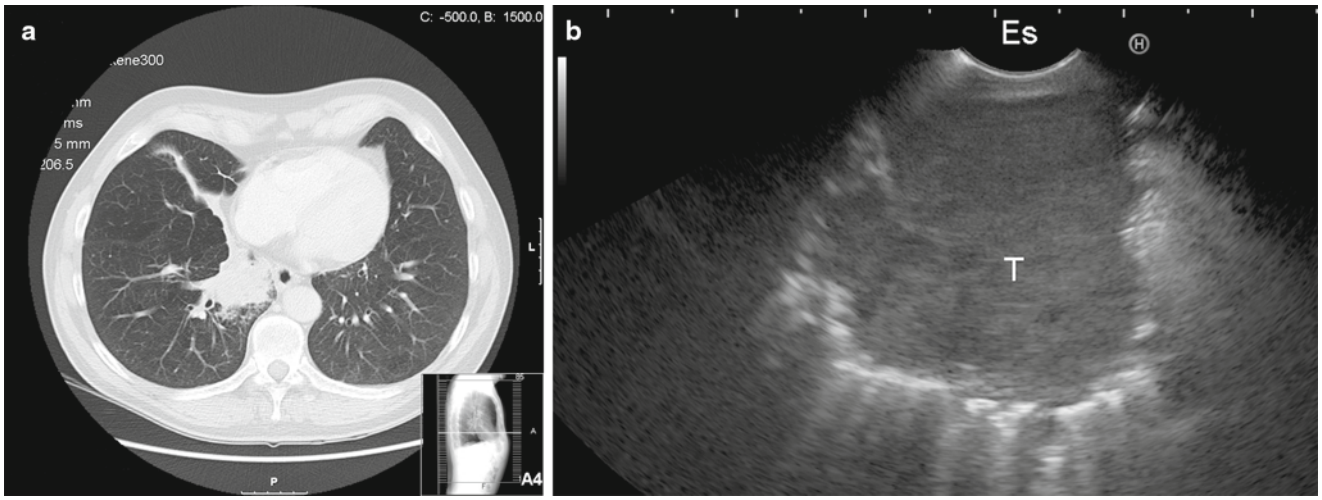

Fig. 19.7 (**a**) CT scan of the chest showing a centrally located right lower lobe tumor. No diagnosis was obtained with bronchoscopy. (**b**) Corresponding EUS image showing the right lower lobe tumor (*T*) from the esophagus (*ES*). The diagnosis squamous cell carcinoma was made by EUS-FNA

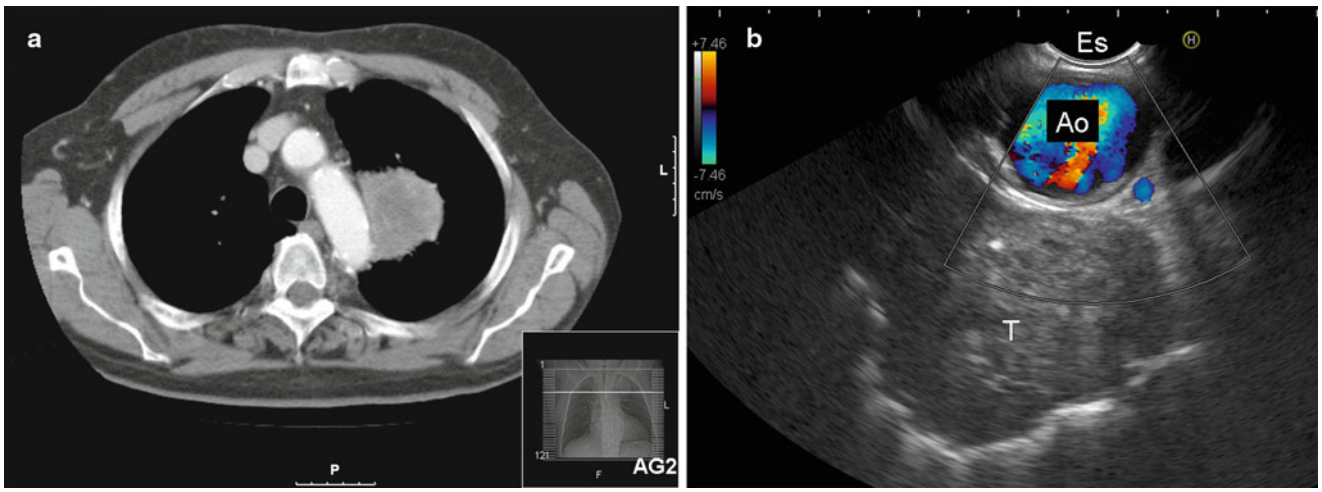

Fig. 19.8 (**a**) CT scan of the chest demonstrating a tumor of the left upper lobe located adjacent to the aorta. (**b**) Corresponding EUS image showing the left upper lobe tumor (*T*). The aorta (*AO*) functions as an ultrasound window. There are no signs of aortic invasion. *ES* esophagus

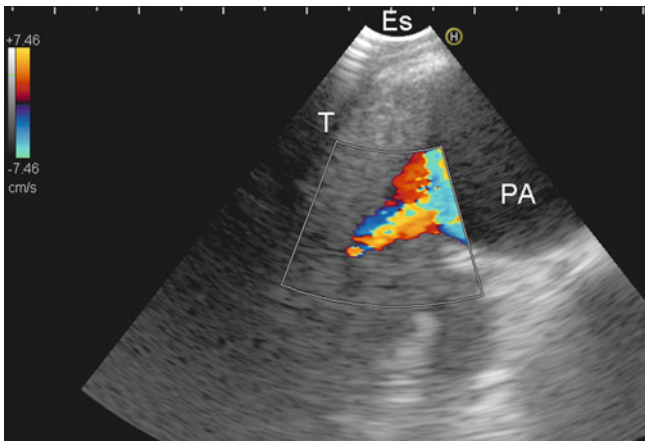

Fig. 19.9 EUS image of centrally located left side tumor (*T*) invading the pulmonary artery (*PA*). Images are compatible with T4 (stage IIIB)

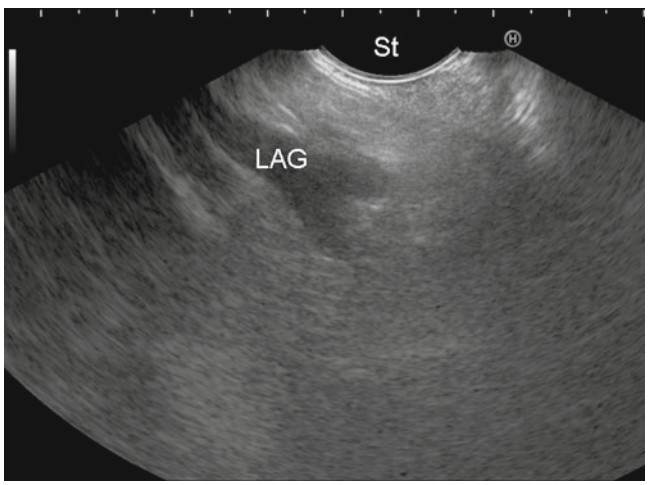

Fig. 19.10 Transgastric EUS image of normal-sized and normal-shaped left adrenal gland (*LAG*). Notice the typical "seagull" shape. *St* stomach

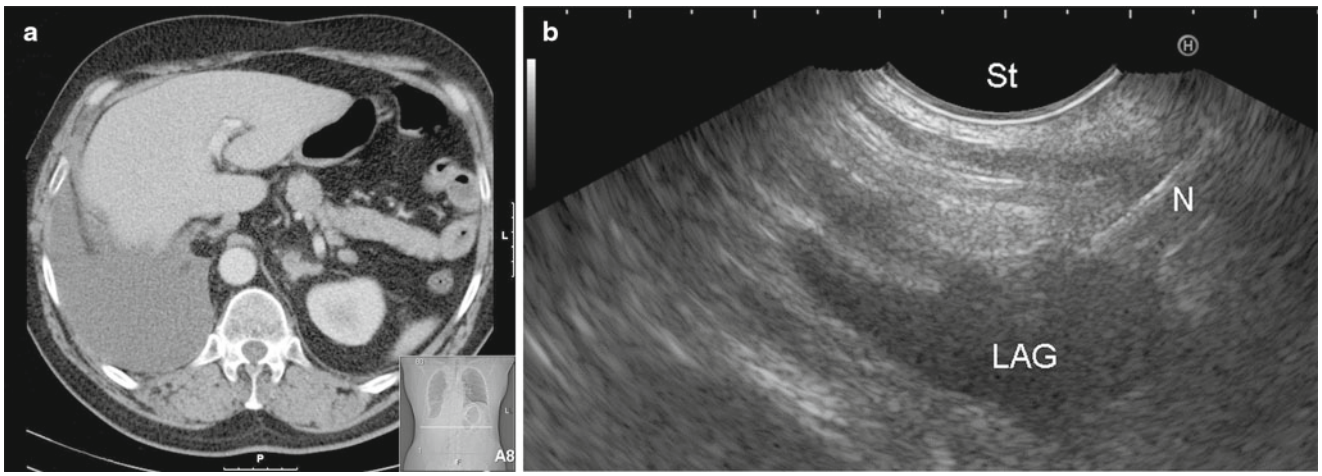

Fig. 19.11 (**a**) CT image of a slightly enlarged, hypodense left adrenal gland in a patient with NSCLC. (**b**) Corresponding EUS images, demonstrating a transgastric needle (*N* needle) aspirate of the left adrenal gland. The typical "seagull shape" is absent (Refs. [1–53])

Endosonography in Lung Cancer Staging Algorithms

EUS is a safe, minimally invasive, and accurate technique to detect mediastinal tumor spread within their diagnostic reach. EUS can prevent 50–70 % of scheduled mediastinoscopies by providing tissue proof of advanced disease in patients with (suspected) lung cancer and enlarged or PET-positive nodes. However, EUS has limitations in excluding malignant nodal involvement. Several studies have shown that a complete endosonographic evaluation – combining an esophageal and endobronchial approach – improves nodal staging versus each of the techniques alone. EUS has a complementary value to both EBUS and mediastinoscopy especially for nodes located in the lower mediastinum and aortopulmonary window. Additionally, mediastinal tumor invasion can be diagnosed as well as left adrenal metastases (Table 19.2). A complete endosonography evaluation of the mediastinum is at least as good as mediastinoscopy but is associated with fewer complications. Therefore, endosonography – and not mediastinoscopy – qualifies as the initial mediastinal tissue staging test. Performing mediastinoscopy after a negative endosonography improves the sensitivity of mediastinal nodal staging from 85 % to 94 %. Whether all patients staged negative by endosonography – or a selected subgroup – should subsequently undergo surgical staging of the mediastinum is under discussion. Ongoing studies focus on predictors for false-negative endosonography results.

Table 19.2 Added value of esophageal to endobronchial ultrasound

Complementary diagnostic reach
– Lower mediastinum: stations 8 and 9
– Aortopulmonary window: station 5 (only in selected cases)
– Para-aortal region: station 6 (transaortal approach)
– Left adrenal gland
– Lung tumors located adjacent to the esophagus
Histology sampling possible (19-gauge, Tru-Cut, Quick core needles)
Well tolerated by patients (no coughing or dyspnea)

Granulomatous Diseases

Sarcoidosis is the most common interstitial lung disease and has pulmonary involvement in around 90 % of patients. Patients with sarcoidosis stage I and II present with enlarged intrathoracic nodes that can be easily detected by EUS. Nodes in patients with sarcoidosis typically present as multiple well-demarcated, well-vascularized nodes with an isoechoic ultrasound pattern. Non-caseating granulomas in patients with sarcoidosis are found by EUS in around 90 % of patients for stage I and 80 % for stage II. Diagnosing sarcoidosis with EUS has a very low complication rate and is not associated with a risk of hemoptysis and pneumothoraces as can occur after taking transbronchial lung biopsies. It is expected that, where available, EUS will largely replace bronchoscopy with transbronchial lung biopsies as the procedure of choice to obtain granulomas. With the increasing availability of endosonography,

mediastinoscopy for the diagnosis of sarcoidosis is rarely indicated. On EUS, tuberculous involved nodes typically present with a hypoechoic center compatible with central necrosis. Samples of fine-needle aspirates also qualify for PCR analysis and culture. Aspirates obtained by EUS can reliably differentiate between sarcoidosis and tuberculosis.

Solitary Mediastinal Masses

Mediastinal masses – without a lung lesion – frequently pose a diagnostic challenge. Posterior mediastinal lesions that are located adjacent to the esophagus can be easily visualized and sampled by EUS. EUS-FNA has been proven to be a useful test for mediastinal lesions in patients with an (previous) extrathoracic cancer. Conflicting results regarding the usefulness of EUS for diagnosing lymphomas have been reported as often larger tissue samples are required to obtain a correct classifying diagnosis. The development of needles with a "biopsy forceps" might overcome this limitation. Bronchogenic and paraesophageal cysts can be visualized well with EUS. Ultrasound features of cysts can verify from echo-free to multiple echo-dense spots depending on the content. Cysts should not be sampled due to the risk of infection and mediastinitis.

Conclusion

Esophageal ultrasound-guided fine-needle aspiration of mediastinal nodes and centrally located lung tumors is a minimally invasive and safe diagnostic technique for the diagnosis and staging of lung cancer, the analysis of posterior mediastinal masses, and the assessment of sarcoidosis. Evaluation of the mediastinum by EUS has an added value to EBUS and mediastinoscopy due to its completely diagnostic reach especially in the lower mediastinum, the aortopulmonary window, and the left adrenal gland. For a completely equipped pulmonary endoscopy suite, knowledge and expertise in esophageal ultrasound is needed.

Suggested Reading

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EBUS Guidance for Peripheral Biopsies

20

Ralf Eberhardt

Background

Even though the risk factors for lung cancer are well established, it remains the leading cause of cancer death in both men and women. Despite its high incidence, signs and symptoms are rarely present. Thus, most patients with an initial diagnosis of lung cancer have advanced stage disease, making a cure with currently available therapies unlikely. In contrast, early diagnosis of lung cancer enables surgical resection with curative intent.

The purpose of lung cancer screening is to provide early diagnosis, which may potentially prevent death from the cancer. Therefore, low-dose computer tomography (LDCT) is normally used, which results in the detection of a higher number of lung cancers with a significantly higher proportion with stage I disease. With the advances in imaging, both computed tomography (CT) and positron emission tomography (FDG-PET) play an increasing role in lung cancer detection, but their use in establishing a definitive diagnosis is limited by the poor specificity and does not allow the ruling out of malignancies. In a recently published meta-analysis of lung cancer screening, however, LDCT also resulted in an increased detection rate of false-positive nodules and more unnecessary thoracotomies for benign lesions.

Even though in patients with a very high pre-test probability for lung cancer referral for lobectomy is still suggested by the guidelines, most of them are poor candidates for a surgical resection due to their co-morbidities. Bronchoscopically guided biopsy therefore remains important as a tool.

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Peripheral Pulmonary Lesions

A solitary pulmonary nodule (SPN) is defined radiologically as an intraparenchymal lung lesion that is less than 3 cm in diameter and is not associated with atelectasis or adenopathy. Peripheral pulmonary lesions with a size of more than 3 cm in diameter are named lung masses. The likelihood of malignancy for SPN between 0.8 and 2.0 cm was previously reported to be about 18%, and for nodules larger than 2.0 cm, about 50%. Therefore, because of the possible presence of lung cancer, the detection of peripheral lesions frequently requires tissue diagnosis in a minimally invasive way.

Although there is no accordance in the guidelines as to which approach is the best for diagnosing peripheral pulmonary nodules, CT-guided transthoracic needle aspiration (TTNA) of the indeterminate pulmonary nodule is a well-established, highly accurate and minimally invasive diagnostic procedure. A pulmonary nodule in virtually any location is accessible to transthoracic needle biopsy. There is a trend toward lower sensitivity for smaller lesions, but overall CT-guided TTNA may result in a diagnosis in 74% up to 96% of patients, again depending on the lesion size and distance to the pleura. However, transthoracic biopsy by CT guidance is associated with exposure to radiation and a significant risk of pneumothorax, with rates of 15–44%.

Transbronchial Biopsy

Bronchoscopy is an established technique in diagnosing lung cancer and has been used in evaluating SPN and masses for more than 30 years. In patients with such nodules, the diagnostic procedure usually performed is a transbronchial biopsy (TBB) under fluoroscopic guidance. However, flexible bronchoscopy has a variable and often poor success rate in sampling pulmonary lesions during a normal endobronchial examination under fluoroscopy.

A. Ernst and F.J.F. Herth (eds.), *Principles and Practice of Interventional Pulmonology*,
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The main limitation of flexible bronchoscopy is the difficulty in successfully obtaining adequate tissue samples for pathological diagnosis. The sensitivity of bronchoscopy for detecting malignancy in a solitary pulmonary nodule depends on the size of the nodule, the proximity of the nodule to the bronchial tree, the success in sampling the nodule and the prevalence of cancer in the study population.

For peripheral lesions between 2.5 and 4.0 cm, a bronchoscopic diagnostic yield of 62% was reported, but the diagnostic sensitivity in patients with suspicion for cancer decreased to less than 40%, if the nodules were smaller than 2.5 cm. Successful biopsies are mostly achieved with fluoroscopic guidance, but especially nodules less than 20 mm in diameter are difficult or impossible to visualise. Thus, for these nodules, Schreiber et al. in a meta-analysis found an overall diagnostic sensitivity of only 33%.

Endobronchial Ultrasound for Peripheral Lesions

Localising small lesions under fluoroscopy is difficult, and alternative diagnostic guidance methods like CT-guided bronchoscopy are logistically more demanding. In a recent trial, CT-guided TBB was not shown to be superior to TBB under fluoroscopic guidance. Therefore, new methods for navigation and localisation are needed. One of these technologies is radial endobronchial ultrasound (EBUS), which can be used to detect pulmonary nodules in the peripheral lung.

Principles and Technique

Ultrasound imaging is almost completely reflected by air in the lung parenchyma, and other radiological imaging seems to be superior in visualising lesions in the peripheral, ventilated lung. In contrast, small-calibre, radial ultrasound probes can be placed through the working channel of a flexible bronchoscope in the periphery of the lung and used for the clinical application of ultrasonography to SPN. Ultrasound probes with an external diameter of 1.4 and 1.7 mm are available from different companies (Fig. 20.1). The so-called *miniprobes* are fragile and have to be handled very delicately.

Fig. 20.1 Radial ultrasound miniprobe (20 MHz UM-S20-17S, Olympus Inc, Tokyo, Japan) introduced via a guide sheath through the working channel of a flexible bronchoscope. On the *right*, guide sheath only without miniprobe (Reprinted with permission from Olympus Europe Holding GmbH, Hamburg, Germany)

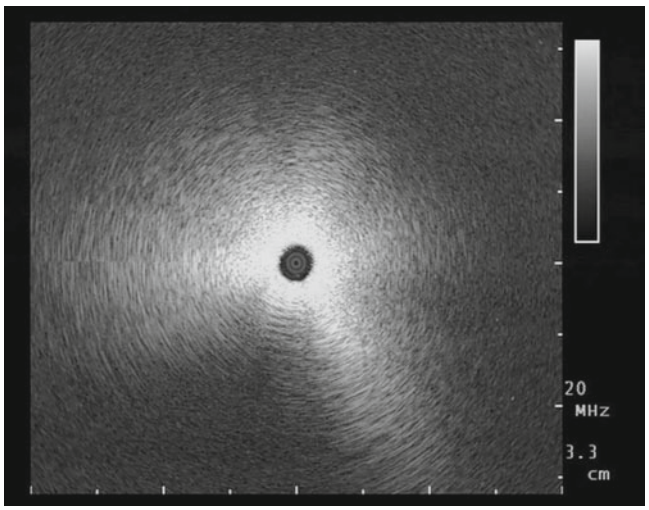

Fig. 20.2 A "snowstorm-like" ultrasound image, characteristic of normal ventilated, peripheral lung

Ultrasound Imaging of Peripheral Lung Lesions

The most commonly used frequency in radial EBUS is 20 MHz, which provides a high resolution and allows detailed imaging of the structure of peripheral lung lesions. Normal air-filled alveolar tissue typically produces a "snowstorm-like" whitish ultrasound image due to differences in impedance (Fig. 20.2). Structures, which are close to the probe but separated by air, are not visible due to the total reflection of the ultrasound waves. If it is possible to reach a peripheral lung lesion with the probe, the ultrasonic picture will change. Solid tumours are usually well differentiated against the lung tissue by a bright border. They appear grey and more homogeneous in the ultrasound image (Fig. 20.3), although necrotic areas and vessels can be seen as circumscribed black areas. Furthermore, the existence of a continuous hyperechoic

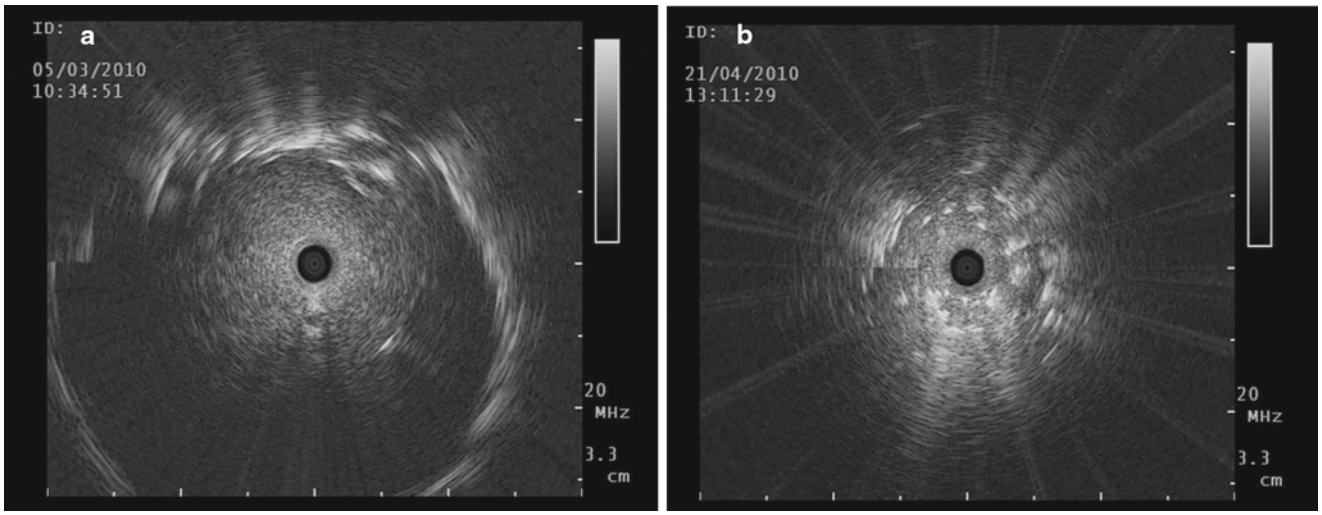

Fig. 20.3 (**a**) Typical ultrasound image of a malignant solid tumour with clear borders. No air bronchogram is seen, which is a distinguishing sign for inflammatory disease or atelectasis; (**b**) white spots are visible centrally and the borders of the lesion are blurred in this benign lesion

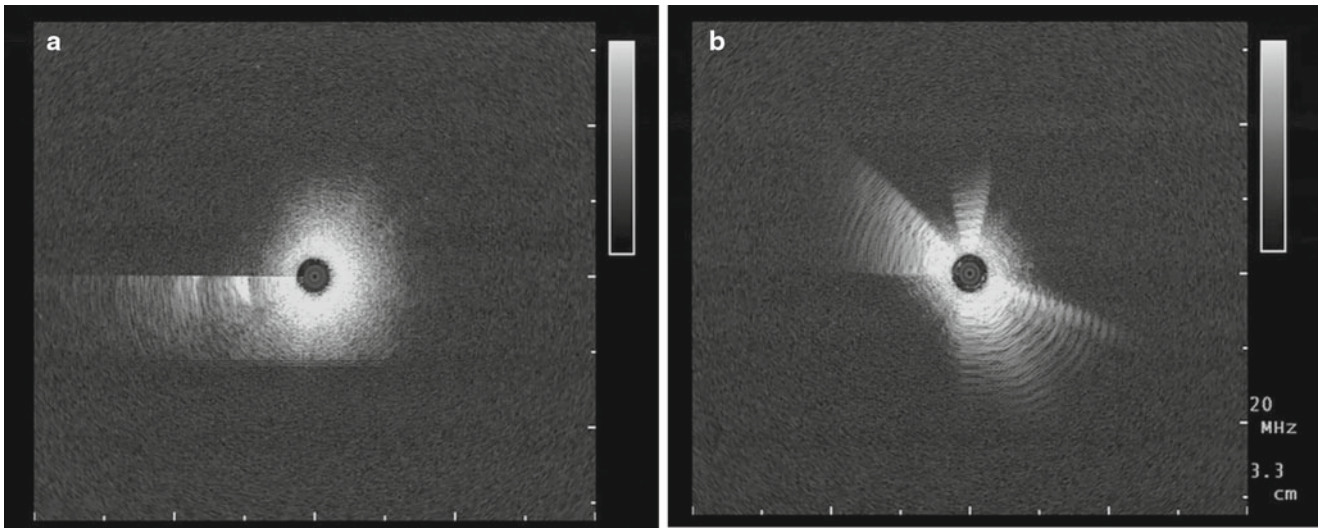

Fig. 20.4 Two specific artefacts which can be observed frequently: (**a**) a motion artefact at 9 o'clock and (**b**) repeating echoes surrounding the miniprobe

margin and absence of a linear-discrete air bronchogram indicate a suspicion for cancer. In contrast, the ultrasound images of inflammatory tissue or atelectasis have an inhomogeneous distribution, caused by the different structures of the lung. Small bronchi containing trapped air are visible as sharp white echo spots, fluid-filled areas also appear dark and borders are slightly blurred (Fig. 20.3).

Imaging Artefacts

The use of EBUS in the peripheral lung is simple, but interpretation of ultrasound images can sometimes be difficult. Fluids appear dark in the ultrasound images, but no Doppler mode is available in the radial ultrasound to identify vessels. To differentiate between necrotic areas and vessels, it is possible to follow the length of the lesion or to look for arterial vascular pulsation concurrent with the patient's heartbeat. Trapped air shows sharp white spots with a "comet tail" sign behind, which looks similar to calcifications.

Further artefacts are possible, and this can lead to false interpretations. The radial image configuration starts at 9 o'clock, so during very quick movements, motion artefacts can be seen there as a sharp line. Strong reflections will create repeating echoes, which can be recognised by their consistent interval distance (Fig. 20.4).

Technique of EBUS Navigation

The EBUS probes have to be advanced like a forceps into the different bronchi, where the lesion is suspected. This can be difficult in the apical segments and has to be performed carefully, because flexion and friction of the probe can damage the transducer and the connecting driving wire. A water-filled balloon is normally not necessary to provide sufficient contact to the surrounding structures when using the radial EBUS in the peripheral airways.

When solid round- or oval-shaped structures are visible, it indicates that the lesion is reached, and the probe is considered to be located within or adjacent to the lesion. After detection of the target, the probes must be removed from the working channel to introduce a biopsy tool for sampling specimens of the area of interest (Fig. 20.1).

Biopsy Tools

Transbronchial forceps biopsy is still the gold standard for sampling specimens from peripheral lung lesions. The tissue biopsy allows both histological and immunohistological examinations. In addition to the TBB, established biopsy tools for diagnosing peripheral lung lesions endoscopically are aspiration, brush sampling or transbronchial needle aspiration (TBNA). It has been shown that the yield will increase, when a cytological sampling is added to the TBB by forceps. Especially the sensitivity of TBNA in diagnosing peripheral lung lesions is greater than that of TBB in all papers in which these two techniques have been compared. In contrast, bronchial washing provides no added benefit to the diagnostic yield in patients undergoing bronchial brushing or TBB.

This applies to conventional bronchoscopy as well as to EBUS guidance. Concerning the different techniques, EBUS-guided TBNA showed the highest diagnostic yield compared with EBUS-guided TBB and bronchial washing. In a retrospective analysis of 155 patients, the yield for TBB in diagnosing SPN was higher, when the probe could be placed within the lesion (83%) compared to SPN in which the probe could only be placed adjacent to the target. No significant differences could be seen in the diagnostic yield for factors such as location, bronchus sign seen on CT, underlying disease, operator and type of EBUS probe used (Fig. 20.5).

Applying TBNA to EBUS-guided bronchoscopy can further increase the diagnostic yield of SPNs without additional risk. The diagnostic advantage of TBNA becomes more obvious if the EBUS probe is only adjacent to the lesions. For malignant lesions, sampling by catheter aspiration was also associated with a higher diagnostic yield than sampling by forceps biopsy alone, in particular when EBUS could not confirm lesion location prior to sampling.

The disadvantages of cytological assessments are the requirement for an experienced cytopathologist and the difficulties in obtaining samples sufficient for immunochemistry.

Flexible cryoprobes which can be used for transbronchial histological sampling through a guide sheath may overcome these problems. After EBUS guidance, big biopsies without crush artefacts can be taken with this new approach, apparently without increased risk for pneumothorax and/or bleeding (Fig. 20.6).

Fluoroscopic Guidance

In 2002, a report on the use of radial EBUS for SPN was first published. This was a prospective study comparing the diagnostic yield of fluoroscopy-guided versus EBUS-guided TBB, and diagnostic material was obtained in 76% with fluoroscopy versus 80% with EBUS guidance. A non-significant trend was observed towards EBUS being better than fluoroscopy for lesions of less than 3 cm in diameter.

Today, the most common additional approach for reaching peripheral lesions with EBUS is the use of fluoroscopy, which aids in directing the EBUS probe towards the peripheral lesion. Once the lesion has been detected in the ultrasound image and confirmed by fluoroscopy, a forceps is then introduced via the working channel of the bronchoscope and directed into the subsegmental bronchus. This is again controlled by fluoroscopy, and TBB can now be taken under fluoroscopic guidance. Even though the EBUS probe has to be removed prior to taking the TBB and this is therefore not a real-time procedure, a high yield can be achieved this way. Another advantage is the possibility to use a bigger forceps under guidance in order to obtain larger biopsy samples.

EBUS via Guide Sheath

Kurimoto first introduced the use of endobronchial ultrasound together with a guide sheath. For this technique, the bronchoscope is first advanced into the target bronchus under direct vision, and then the EBUS probe within a guide sheath is introduced via the working channel of the bronchoscope. A standard bronchoscope with a working channel of 2.0-mm diameter as well as a catheter with diameter of 1.9 mm can be used for the 1.4-mm probe. For the larger ultrasound probes of 1.7 mm, a bronchoscope with a working channel of 2.8 mm or larger and a guide sheath of 2.7 mm should be used. Now EBUS imaging confirms that the probe within the guide sheath has reached the lesion, and the EBUS probe is removed leaving the guide sheath in place. This guide sheath can now be used as an extended working channel in order to sample the lesion with either forceps, brush or curette. It is possible to use additional imaging with fluoroscopy to obtain the specimens. A retrospective analysis showed the optimum number of biopsy specimens with ultrasound guidance to be at least five.

In cases where the SPN cannot be visualised by EBUS, the probe should be removed from the guide sheath and a double-hinged curette can be inserted. This curette can now be manipulated under fluoroscopic guidance to identify the

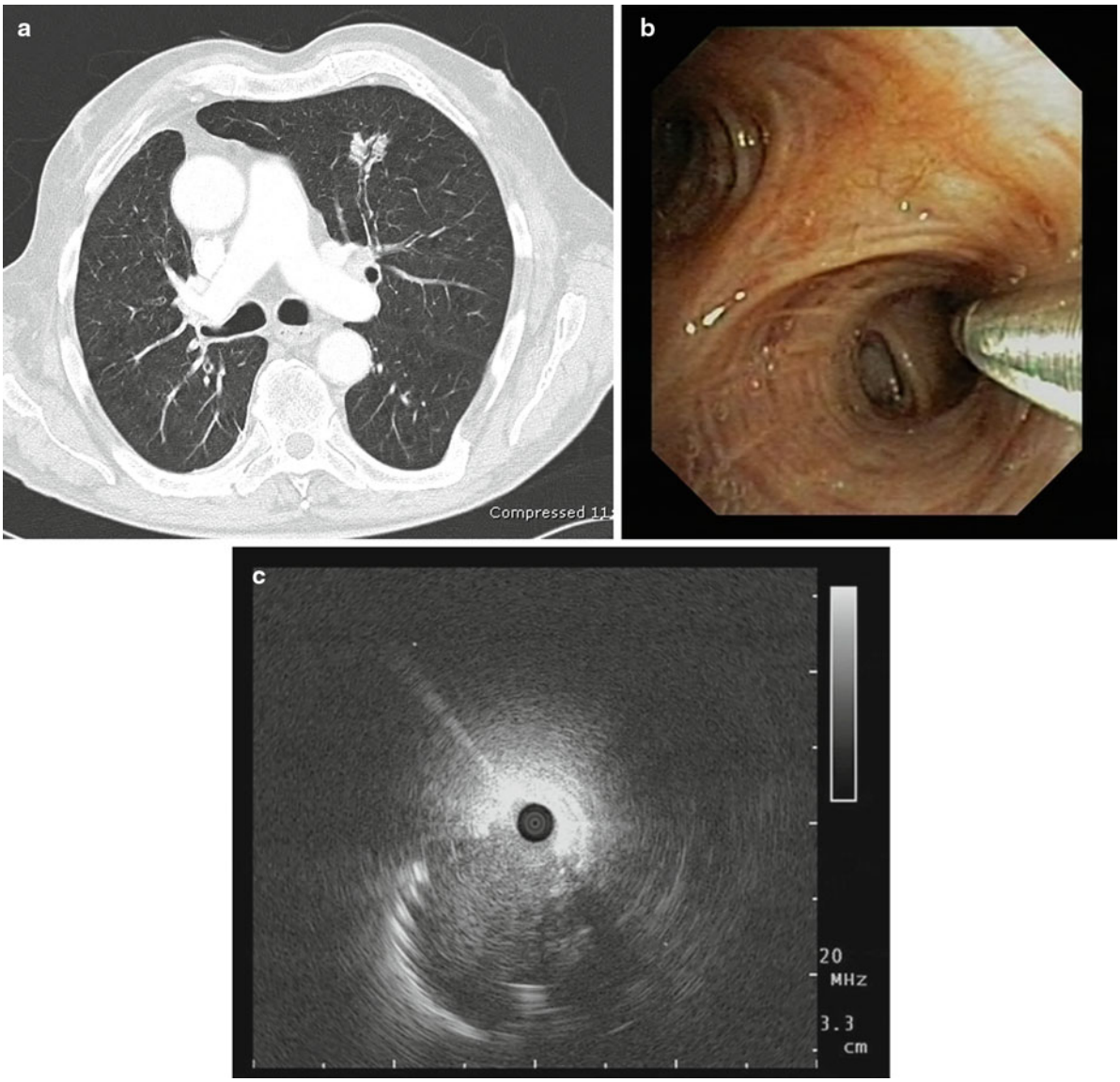

Fig. 20.5 (**a**) Bronchus sign: a bronchus leads directly to the peripheral nodule in the left upper lobe; (**b**, **c**) after introducing the miniprobe under endoscopic control in the anterior segmental bronchus, the lesion could be detected. Although the ultrasound probe could be placed only adjacent to the lesion, a non-small cell lung cancer was diagnosed with transbronchial forceps biopsy under fluoroscopic control (Part (a) courtesy of Prof. Dr. Claus P Heußel, Department of Diagnostic and Interventional Radiology, Thoraxklinik at the University of Heidelberg)

appropriate bronchus. Once it has been found, the curette is removed again and the EBUS probe is advanced to confirm the correct position on ultrasonographic picture (Fig. 20.7).

EBUS in Diagnosing Small or Non-visible Peripheral Pulmonary Lesions

Nodules less than 3 cm frequently cannot be visualised fluoroscopically. One prospective study assessed the diagnostic yield of EBUS-guided TBB in fluoroscopically invisible SPN and was able to show that in 80% the lesion was localised with EBUS (mean diameter of 2.2 cm) and a diagnosis was established by biopsy in 70%. EBUS can hence be used as an alternative to fluoroscopy in providing image guidance for TBB. *Yoshikawa* could further confirm the usefulness of endobronchial ultrasonography as a guide for diagnosing peripheral pulmonary lesions without the use of radiographic fluoroscopy. Seventy-six of 123 SPN (61.8%) were diagnosed by EBUS-guide sheath alone. In this study, the diagnostic yield for lesions >20 mm was significantly higher than for those ≤ 20 mm in diameter. In a prospective study, 100 patients with SPN less than 20 mm were assessed with the guide sheath technique. Although the diagnosis was established only in 46 patients (46%) by EBUS-guided TBB, for those lesions which were detected by endobronchial ultrasound, the diagnostic success was 69%, which is similar to other studies. Therefore, ultrasound guidance may be

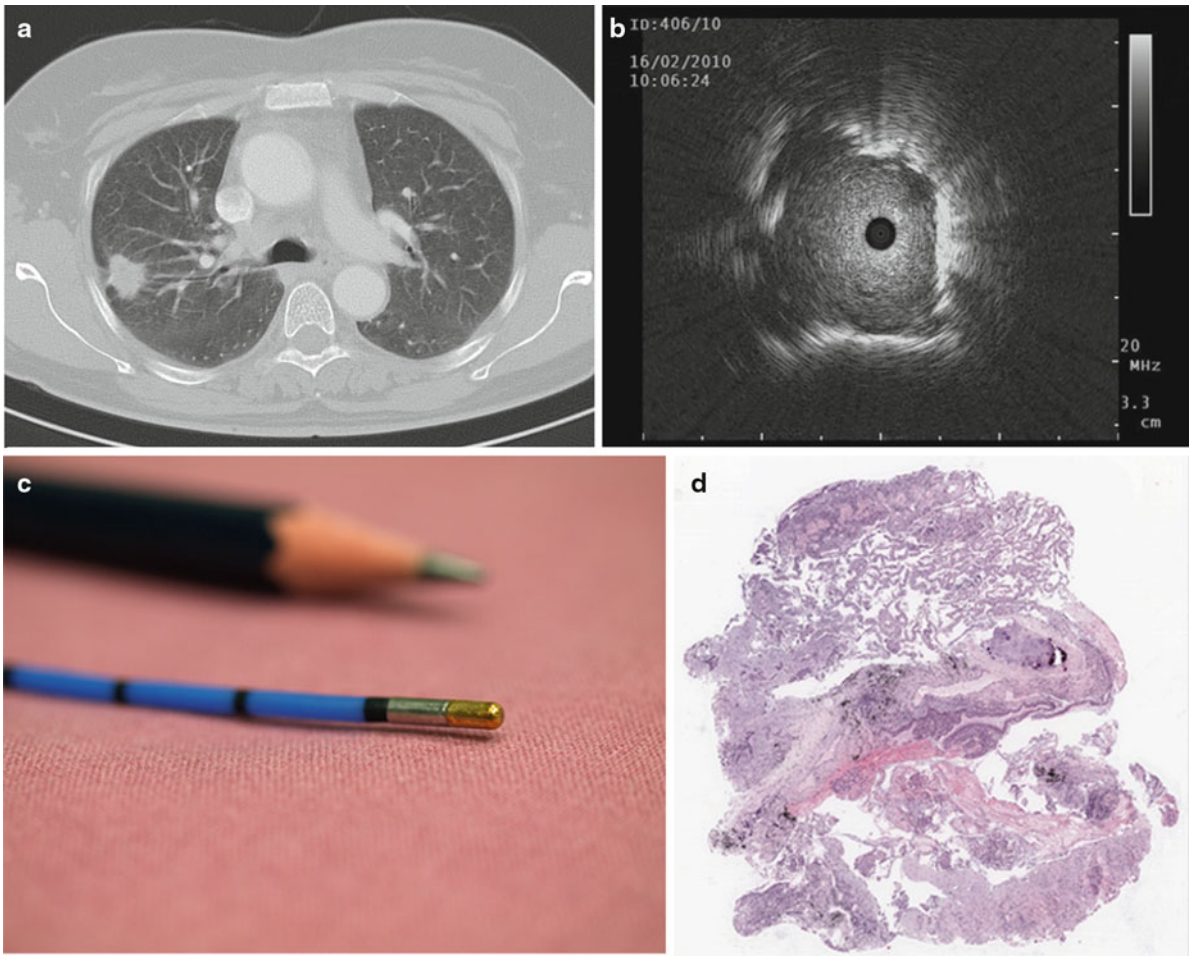

Fig. 20.6 (**a**) CT scan of a 50-year-old female with a solitary pulmonary nodule in the right upper lobe. (**b**, **c**) The lesion was detected with an EBUS miniprobe, and a cryobiopsy was taken with a flexible cryoprobe (no. 120416-037, 1.9-mm external diameter, length 900 mm, Erbe Medizintechnik, Tübingen, Germany) via guide sheath. (**d**) The pathologist estimated a large biopsy of excellent quality without any crush artefacts (HE staining). The final diagnosis established by EBUS-guided cryobiopsy was a micropapillary adenocarcinoma (Part (a) courtesy of Prof. Dr. Claus P Heußel, Department of Diagnostic and Interventional Radiology, Thoraxklinik at the University of Heidelberg; part (c) reprinted with kind permission of Horst Bryant, Heidelberg, Germany; part (d) courtesy of Prof. Dr. Philipp A. Schnabel, Department of Pathology, University of Heidelberg)

more successful than fluoroscopic guidance in sampling non-visible or small peripheral lesions.

Clinical Review and Meta-analysis of EBUS

In a recently published systematic review and meta-analysis, 13 studies and 1.090 patients undergoing EBUS-guided bronchoscopy for diagnosing peripheral lung lesions were included. Although significant inter-study variation in the EBUS method was noted, *Steinfort* found a pooled sensitivity of 73% and specificity of 100% for radial EBUS. Therefore, endobronchial ultrasound is a safe and relatively accurate tool in the investigation of SPN, increasing the likelihood of a diagnosis and decreasing the need for surgical biopsy (Table 20.1). Diagnostic sensitivity of EBUS may be influenced by the prevalence of malignancy in the patient cohort being examined and by lesion size.

In the area of bronchology, randomised studies are rare; however, randomised controlled trial is necessary to directly compare different procedural approaches for the investigation of peripheral lung lesions (Fig. 20.8).

Combination of Ultrasound with Other Guidance Techniques

EBUS enables direct visualisation of the target lesion before attempting biopsy. However, EBUS lacks a navigation system and requires the operator to manoeuvre the bronchoscope blindly to the lesion with the knowledge of prior radiological investigations such as CT scans. Hence, the combination of EBUS with other guidance techniques may provide a better yield for SPN.

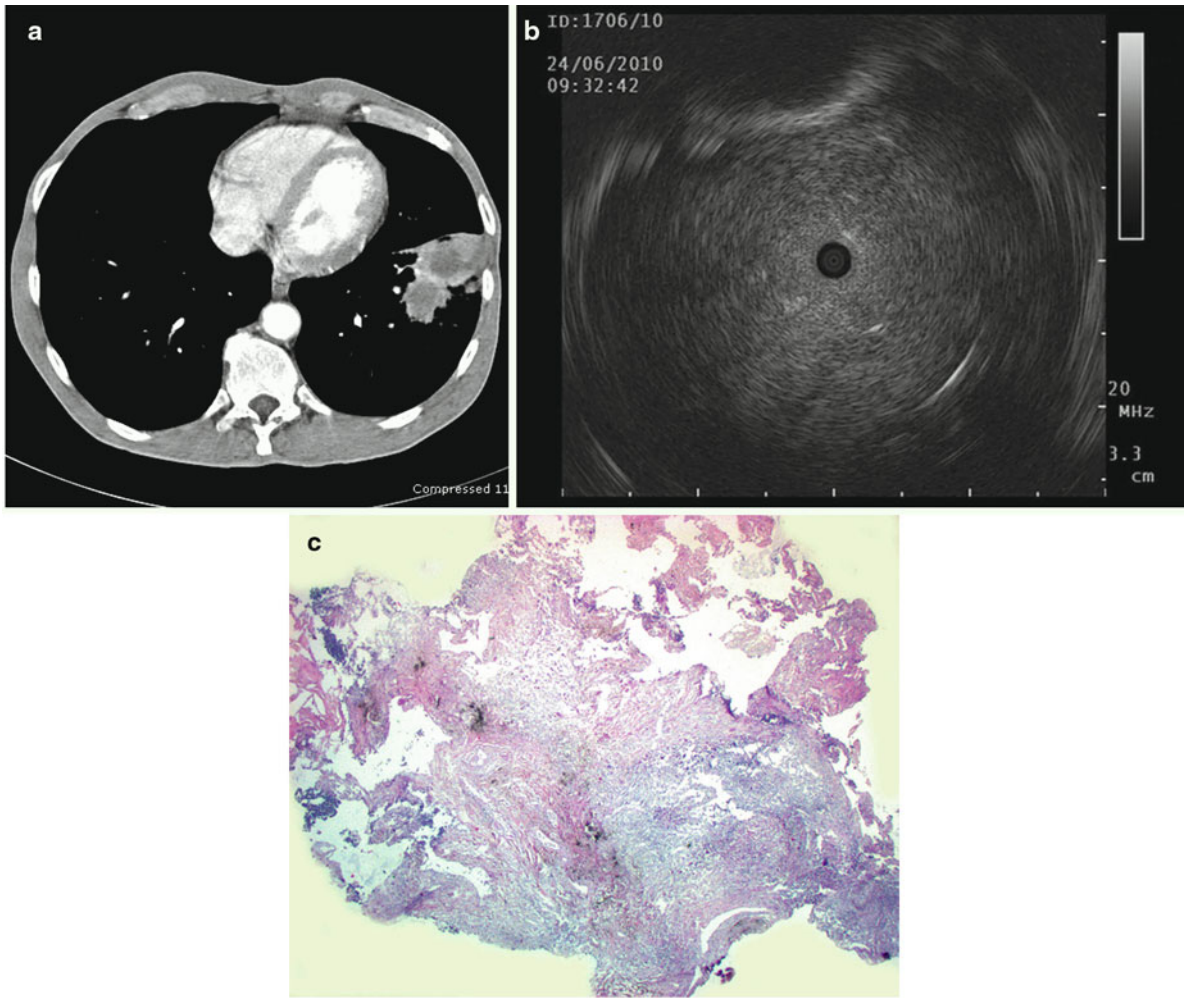

Fig. 20.7 (**a**) A 58-year-old male with a pulmonary lesion in the left lower lobe, (**b**) corresponding ultrasound image with homogeneous structure and clear margins suspicious of malignancy, (**c**) histological cross section of transbronchial forceps biopsy shows necrotic inflammation. The diagnosis of lung abscess was confirmed by surgical resection of the lesion (Part (a) courtesy of Prof. Dr. Claus P Heußel, Department of Diagnostic and Interventional Radiology, Thoraxklinik at the University of Heidelberg; part (d) courtesy of Prof. Dr. Philipp A. Schnabel, Department of Pathology, University of Heidelberg)

Virtual Bronchoscopy

Ultrathin bronchoscopes with an external diameter of 2.8 mm have been used in clinical practice since 2004 and can be advanced to more peripheral bronchi than a standard bronchoscope. Virtual bronchoscopy (VB), a novel CT-based imaging technique, can reconstruct helical CT images to display a three-dimensional rendering and therefore can be used for non-invasive intraluminal evaluation of the tracheobronchial tree. The VB represents the pathway that was selected during the planning process (Fig. 20.9). The usefulness of VB navigation has been reported for CT-guided TBB using an ultrathin bronchoscope. However, this procedure has the disadvantages of excessive radiation exposure from CT and of occupying the CT room for approximately 1 h.

Since small-calibre radial ultrasound probes are available, combining EBUS guidance through the working channel of an ultrathin bronchoscope may overcome the limitations of CT-guided TBB. *Asahina* et al. could demonstrate the feasibility, safety and efficacy of this endoscopic approach. Diagnostic sensitivities were 44.4% for pulmonary lesions < 20 mm and 91.7% for SPN from 20 to 30 mm in mean diameter.

Electromagnetic Navigation

The electromagnetic navigation system (InReach, superDimension Inc., Minneapolis, USA) is a localisation device that assists in placing endobronchial accessories (e.g. forceps,

Table 20.1 Diagnostic yield of EBUS-guided diagnosis of peripheral lung lesions

Author/year	Number of patients	Prevalence of cancer (%)	Additional guidance technique and/or used biopsy tools	Diagnostic yield (%)
Herth 2002	50	84	No additional guidance technique TBB	80
Kurimoto 2004	150	66	Fluoroscopy Guide sheath/TBB or brushing	77
Shirakawa 2004	50	50	Fluoroscopy Guide sheath/TBB and/or brushing	71[a]
Paone 2005	87	67	No additional guidance technique TBB	78
Asahina 2005	30	63	Virtual bronchoscopy + fluoroscopy Guide sheath/TBB + brushing	63
Herth 2006	54 non-visible	57	No additional guidance technique Guide sheath/TBB	70
Eberhardt 2007	39	69	No additional guidance technique Guide sheath/TBB	69
Yoshikawa 2007	121	84	± Fluoroscopy Guide sheath/TBB and/or brushing	86
Yamada 2007	158	68	Fluoroscopy Guide sheath/TBB + brushing	67
Dooms 2007	50	Unknown	No additional guidance technique TBB	62
Fielding 2008	140	50	Fluoroscopy Guide sheath/TBB + brushing	66
Asano 2008	31	Unknown	Virtual bronchoscopy and fluoroscopy Guide sheath/TBB	84
Huang 2009	83	78	No additional guidance technique Distance measured/TBB ± brushing ± bronchial washing	53
Eberhardt 2009	100 ≤ 20 mm	61	No additional guidance technique Guide sheath/TBB	46
Steinfort 2010	1,090 meta-analysis	72	All	73[a]

[a]Sensitivity of diagnosing lung cancer, *TBB* transbronchial biopsies

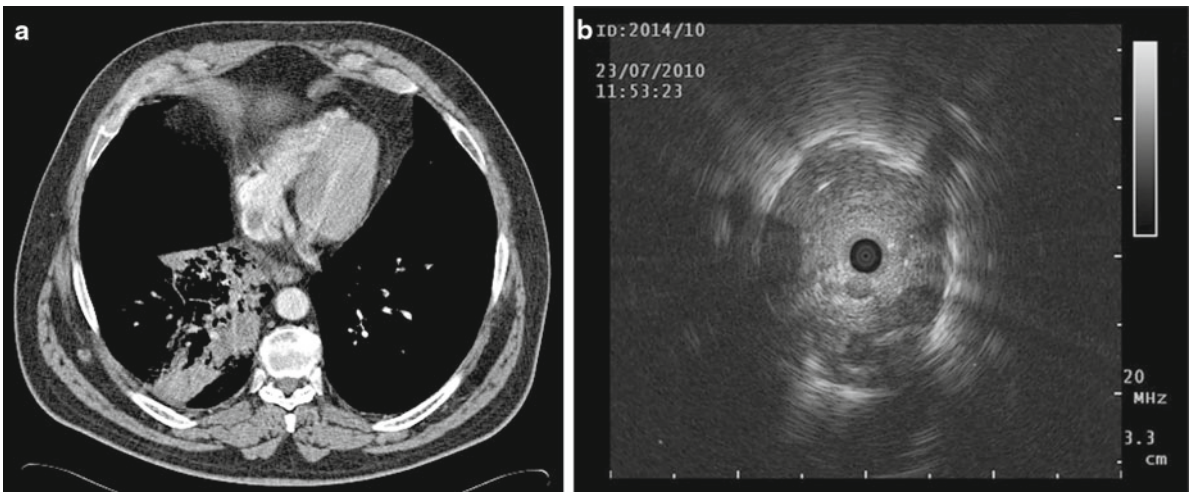

Fig. 20.8 Aspiration pneumonia in the right lower lobe. (**a**) CT scan, (**b**) corresponding ultrasound image with solid inflammatory and necrotic tissue (Courtesy of Prof. Dr. Claus P Heußel, Department of Diagnostic and Interventional Radiology, Thoraxklinik at the University of Heidelberg)

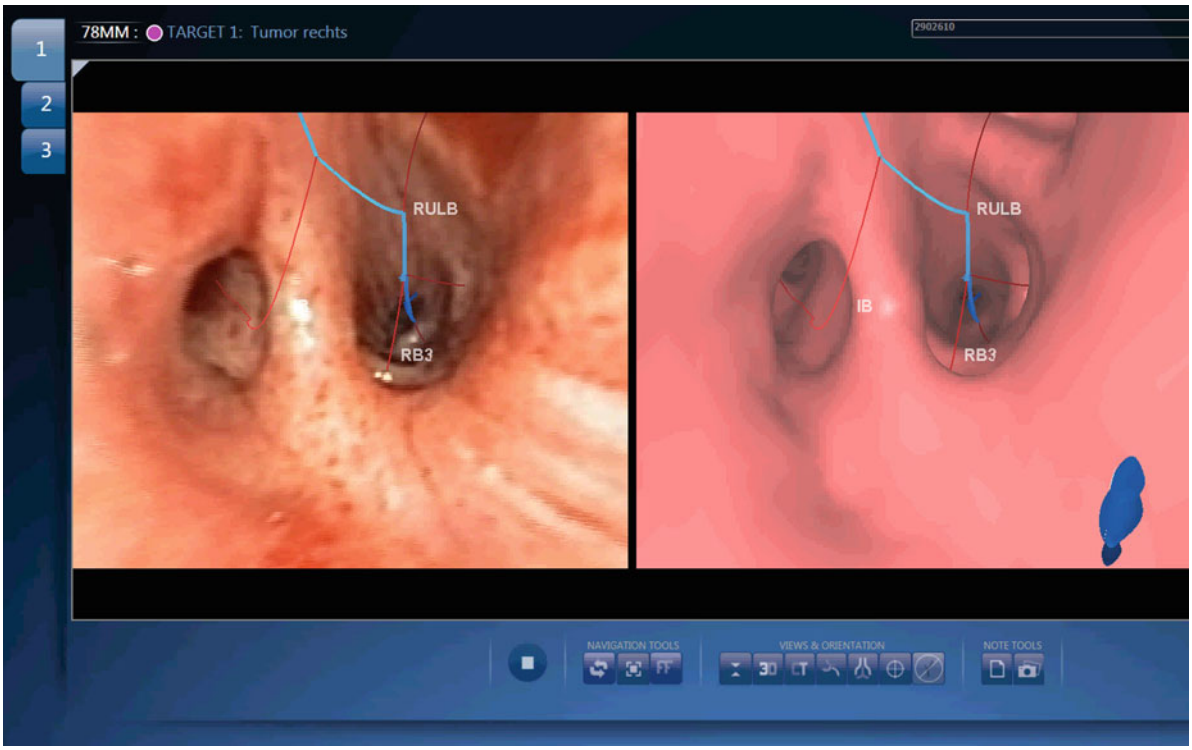

Fig. 20.9 During bronchoscopy, the virtual bronchoscopy images are matched to the real bronchoscopic video to provide procedural guidance to the lesion (Lungpoint® navigation system, Broncus Technologies, Inc., Mountain View, CA, USA). The pre-defined pathway to the target is the *blue line*

brush and needle) in the desired areas of the lung. Electromagnetic-navigation-guided bronchoscopy (ENB) consists of four components: The system uses low-frequency electromagnetic waves, which are emitted from an electromagnetic board placed under the bronchoscopy table mattress. A 1-mm diameter, 8-mm-long sensor probe mounted on the tip of a flexible metal cable constitutes the main assembly of the device (locatable guide). The fully retractable probe is incorporated into a flexible catheter (serving as an extended working channel), which, once placed in the desired location, creates an easy access for bronchoscopic accessories. The computer software and monitor allow the bronchoscopist to view the reconstructed three-dimensional computer tomography (CT) scans of the object's anatomy in coronal, sagittal and axial views together with superimposed graphic information depicting the position of the sensor probe.

This system enables real-time navigation guidance within the lungs to endobronchially invisible targets (Fig. 20.10). ENB lacks a mean to directly visualise the lesion before biopsy, and combining endobronchial ultrasound and electromagnetic navigation improves the diagnostic yield of flexible bronchoscopy in peripheral lung lesions without compromising safety. We could demonstrate in a randomised trial that combined EBUS and ENB overcome each individual technique's limitation. The diagnostic yield of the combined procedure (88%) was greater than either EBUS (69%) or ENB alone (59%).

Multimodality diagnosis with the combined use of EBUS and ENB has pushed the diagnostic yield of flexible bronchoscopic procedures closer to the sensitivity obtainable through either transthoracic CT-guided or surgical biopsies. These techniques may in the future provide a means for therapeutic interventions to inoperable tumour patients. The successful treatment of a peripheral pulmonary tumour by electromagnetically navigated and EBUS-controlled brachytherapy has been reported recently.

Future Applications

Bronchoscopy, as a central technique in diagnosing lung cancer, has the potential to apply endoscopic therapy to small lung lesions in a minimally invasive way in patients with high risk for surgery. Therefore, new guidance techniques like virtual bronchoscopy, electromagnetic navigation as well as radial endobronchial ultrasound are now available. Coupled with a new generation of steerable instruments, a much more reliable means of approaching peripheral lung

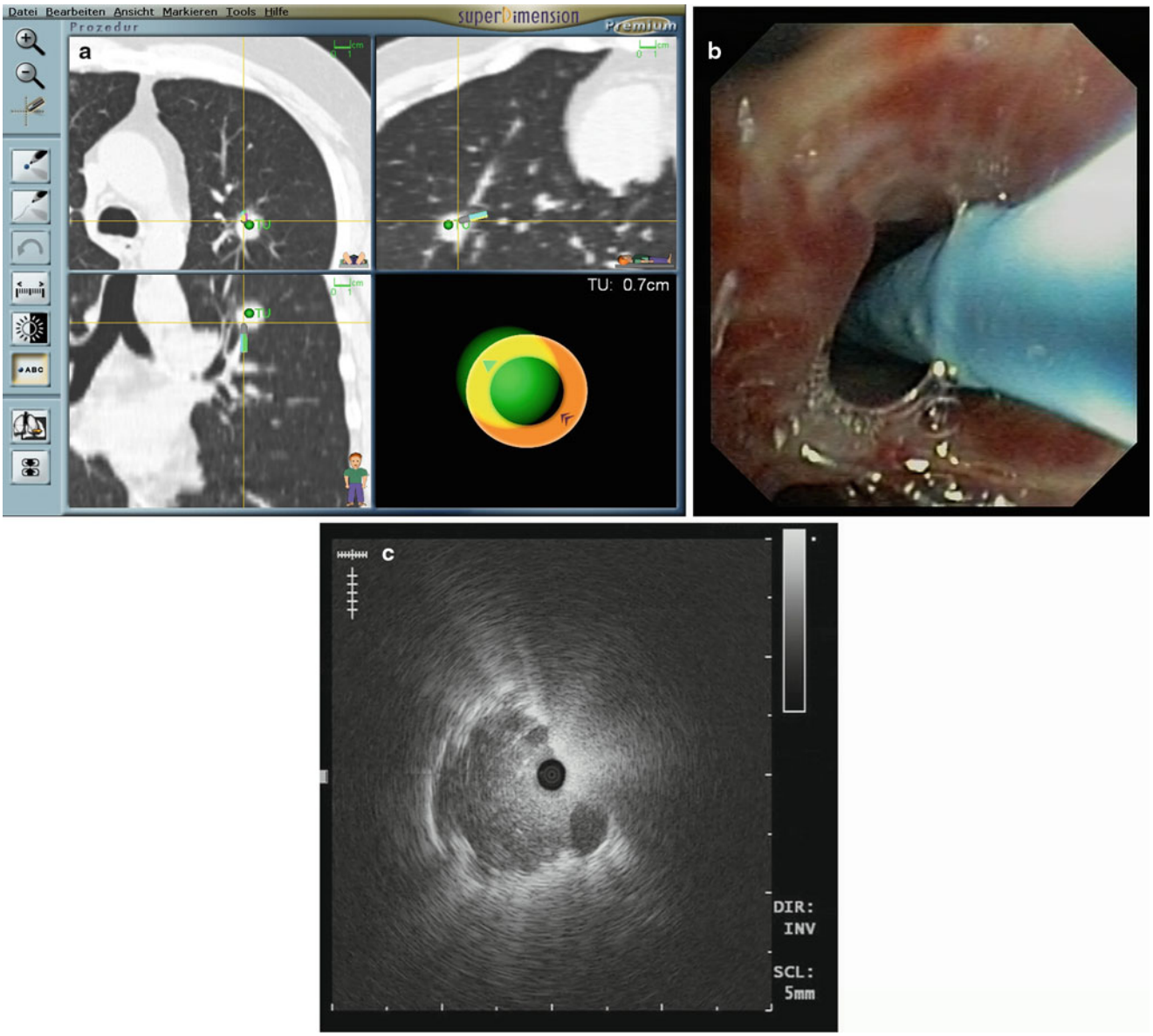

Fig. 20.10 Small peripheral lesion suspicious for lung cancer in the lobe: (**a**) typical screen of an electromagnetic navigation system (InReach, superDimension Inc., Minneapolis, USA). The locatable guide is navigated to the lesion; the distance from the tip to the marked centre (navigation error) is 0.5 cm, (**b**) corresponding endoscopic view. (**c**) Confirmation of the position of the extended working channel inside the lesion by EBUS radial probe

lesions endoscopically finally seems within reach. However, radial EBUS is the only tool which can positively confirm the contact with such a lesion.

Instead of using EBUS with other guidance techniques purely as a diagnostic tool, these techniques may provide an option for therapeutic interventions to inoperable lung cancer patients. Bronchoscopic-guided fiducial marker placement for robotic stereotactic radiosurgery and ENB-guided endoluminal brachytherapy for endoscopic therapeutic management as well as minimally invasive radiotherapy in selected patients are already feasible today. The first flexible and cooled radiofrequency ablation probes are in development.

An early application of endoscopic radiofrequency ablation of small pulmonary nodules or the curative treatment of peripheral lung lesions in non-surgical lung cancer patients is handing treatment options back to the pulmonologist. In the future, the goal should be to diagnose and to treat early stages of lung cancer endoscopically in the same procedure, and radial endobronchial ultrasound will play a decisive role in this field.

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Autofluorescence Bronchoscopy and Narrow Band Imaging

21

Pyng Lee

Introduction

Despite advances in radiological imaging (CT and positron-emission tomography), surgical techniques and postoperative management, radiotherapy delivery, and new chemotherapeutic agents, long-term survival from lung cancer remains poor and has not improved significantly over the last 20 years. Although major potential for lung cancer prevention exists, complete eradication of smoking proves difficult, and the risk of lung cancer remains high in former smokers. The key to improving lung cancer survival is to detect it at an earlier stage, and a recent CT screening trial reports 10-year survival in excess of 80% for clinically stage I parenchymal tumors if intervened early. However, CT for early central airway cancer detection remains poor.

Majority of lung cancers that arise from peripheral airways and lung parenchyma are adenocarcinomas that can be detected by CT, while those arising from central airways are usually squamous cell carcinomas that can be accessed using the bronchoscope. Based on necropsy study of smokers, Auberbach and coworkers postulated that squamous cell carcinomas arose from preinvasive lesions that affected the central airways. The hypothesis that squamous cell carcinogenesis progresses in a stepwise manner where the epithelium changes from normal to hyperplasia; metaplasia; mild, moderate, and severe dysplasia; carcinoma in situ (CIS); and finally to invasive carcinoma is supported by sputum cytology studies where 10% of moderate dysplasia and 40–83% of severe dysplasia advance to invasive lung cancer. The preinvasive lesion represents a potential target for improving patient survival if intervened early. Tumor localization is therefore pivotal in the management of central type early lung cancer (CELC), and conventional diagnostic tools such as CT and white-light bronchoscopy (WLB) lack sensitivity since these lesions demonstrate subtle changes and are generally less than 1.5 mm thick.

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Fluorescence Imaging

Early studies dating back to 1933 and 1943 demonstrated that tissues emitted fluorescence when excited by ultraviolet light. Lycette in 1965 noted a difference in the intensity of autofluorescence between normal and cancerous tissue. When these tissues were excited at 330 nm wavelength, they showed emission in the 360–600 nm range, but fluorescence intensity of tumor was lower than normal tissue. Tissue autofluorescence depends on the concentration of endogenous fluorophores (flavins and porphyrin) as well as the microenvironments between tumor and normal tissues. As the intensity of tumor autofluorescence is weak, some investigators have used hematoporphyrin derivatives, which are preferentially accumulated in tumor to induce red fluorescence and accentuated by endoscopic laser illumination. Notwithstanding that photodynamic diagnosis improves CELC detection it cannot be used routinely due to cost and photosensitivity.

When bronchial surface is illuminated by light, light is absorbed, reflected, backscattered, or induce fluorescence. Reflectance imaging (e.g., WLB) defines structural features of bronchial epithelium and discriminates normal from abnormal. WLB has led to the detection of early hilar lung cancer, and endoscopic features of dysplasia and CIS have been described. However, Woolner and coworkers have reported that only a third of patients with CIS could be identified with this modality.

Autofluorescence bronchoscopy (AF) that exploits differences in fluorescence properties of normal and abnormal bronchial mucosa can facilitate the detection of preinvasive neoplasia which may otherwise be invisible on WLB. Laser-induced fluorescence endoscopy (LIFE) (Xillix Technologies, Canada) is a device that enhances the detection of preneoplastic lesions by capturing differences in autofluorescence

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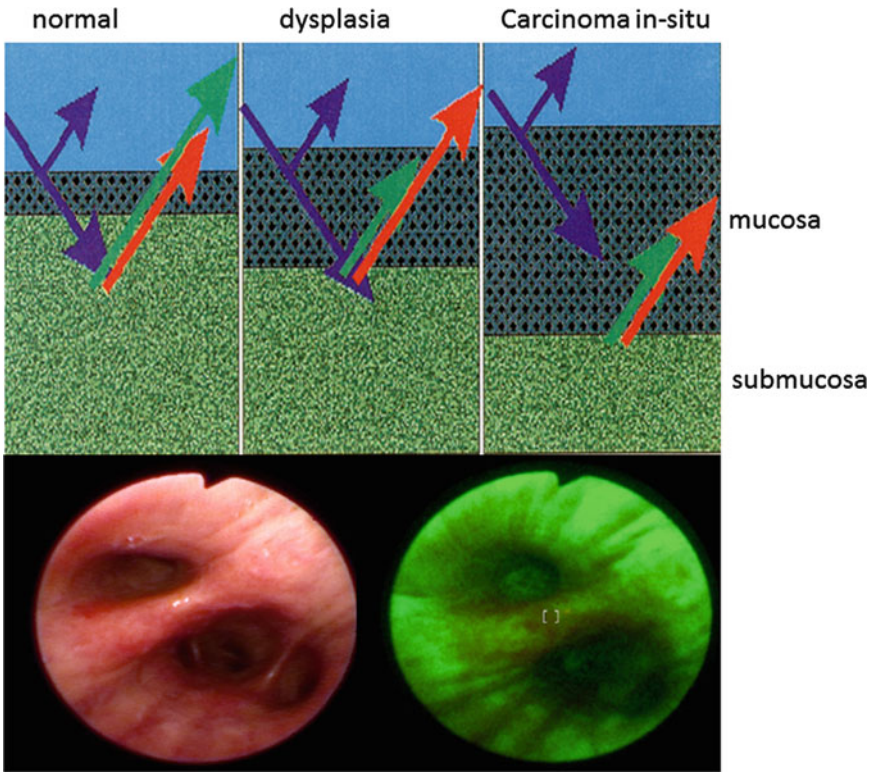

Fig. 21.1 Principles of autofluorescence: green fluorescence is emitted by normal bronchial tissue when excited by blue light, cancer shows decreased green fluorescence due to increased epithelial thickness and vascularity

emitted by normal, preneoplastic, or early malignant tissue when excited by monochromatic blue light (442 nm). Normal bronchial tissue emits green fluorescence (500–600 nm) when excited by blue light, while cancer shows decrease in green fluorescence due to increased epithelial thickness and vascularity (Fig. 21.1). The first LIFE-Lung system uses helium-cadmium laser for illumination; LIFE-Lung II employs a filtered xenon lamp to produce blue light with two image-intensified charge-coupled device sensors: one to capture emitted fluorescence in the green (480–520 nm) and the other in the red (625 nm) spectra. Clinical studies with LIFE have shown increased sensitivity for the localization of lesions with moderate dysplasia and worse; however, difficulties in distinguishing benign epithelial changes such as bronchitis, inflammation, or fibrosis from previous biopsy or endobronchial intervention from preinvasive lesions have led to extensive biopsy with consequent greater health costs, longer procedural time, and higher incidence of procedure-related bronchitis. Notably as high as a third of bronchial lesions with abnormal fluorescence were false-positives when correlated with pathology. Spectral differences between 500 and 700 nm observed for normal, preneoplastic, and neoplastic tissues allow the development of AF-reflectance imaging devices such as Storz D-light (Karl Storz, Germany) and Onco-LIFE (Onco-LIFE Endoscopic Light Source and Video Camera; Novadaq Technologies) based on fiber-optic technology and SAFE 3000 (Pentax, Japan) and AFI (Olympus, Japan) on video endoscopy.

Clinical studies (Table 21.1) using these devices have generally demonstrated improved sensitivity of AF (1.3–6.4 times) over WLB for the detection of preinvasive lesions, also in patients with abnormal sputum cytology. AF appears to be better at defining tumor margins and may add useful information in preoperative surgical planning as well as in targeting the area for endoscopic treatment (Fig. 21.2).

With the advent of the video bronchoscope that has a miniature charge couple device built in its tip which delivers clearer images, sensitivity for premalignant lesions has correspondingly improved without compromising its specificity. Chhajed et al. showed that the addition of video bronchoscopy to LIFE could better select sites for biopsy. However, the procedure required a change of scopes and represented a source of discomfort to the patient and inconvenience to the bronchoscopist. AFI is a video bronchoscope that displays a composite image by integrating three signals: autofluorescence caused by excitation light (395–445 nm), green and red light signals by respective green (550 nm), and red (610 nm) wavelengths. Since hemoglobin absorbs green and minimal red light, in areas with high hemoglobin due to increased vascularity, a feature of dysplasia rather than bronchitis, Chiyo and coworkers showed that AFI was superior to LIFE in discriminating preinvasive and malignant lesions from

Table 21.1 Sensitivity and specificity of autofluorescence bronchoscopy for airway dysplasia

Authors	Equipment	Sensitivity sequential procedure	Specificity sequential procedure
Lam et al. [7]	BF, LIFE	0.56 (WLB + LIFE)	0.66 (WLB + LIFE)
Hirsch et al. [8]	BF, LIFE	0.79 (WLB + LIFE)	0.29 (WLB + LIFE)
Edell et al. [9]	BF, Onco-LIFE	0.74 (WLB + Onco-LIFE)	0.75 (WLB + Onco-LIFE)
Haussinger et al. [10]	BF, D-Light	0.82 (WLB + D-Light)	0.58 (WLB + D-light)
Chhajed et al. [11]	VE, LIFE	0.72 VE/0.96 LIFE	0.53 VE/0.23 LIFE
Chiyo et al. [12]	VE, LIFE, AFI	0.56 VE/0.97 LIFE/0.8 AFI	0.5 VE/0.37 LIFE/0.83 AFI
Ikeda et al. [13]	VE, SAFE	0.65 VE/0.90 SAFE	0.49 VE/0.47 SAFE
Lee et al. [14]	VE, SAFE	0.86 dual image	0.94 dual image

BF bronchofiberscope, *VE* video bronchoscope

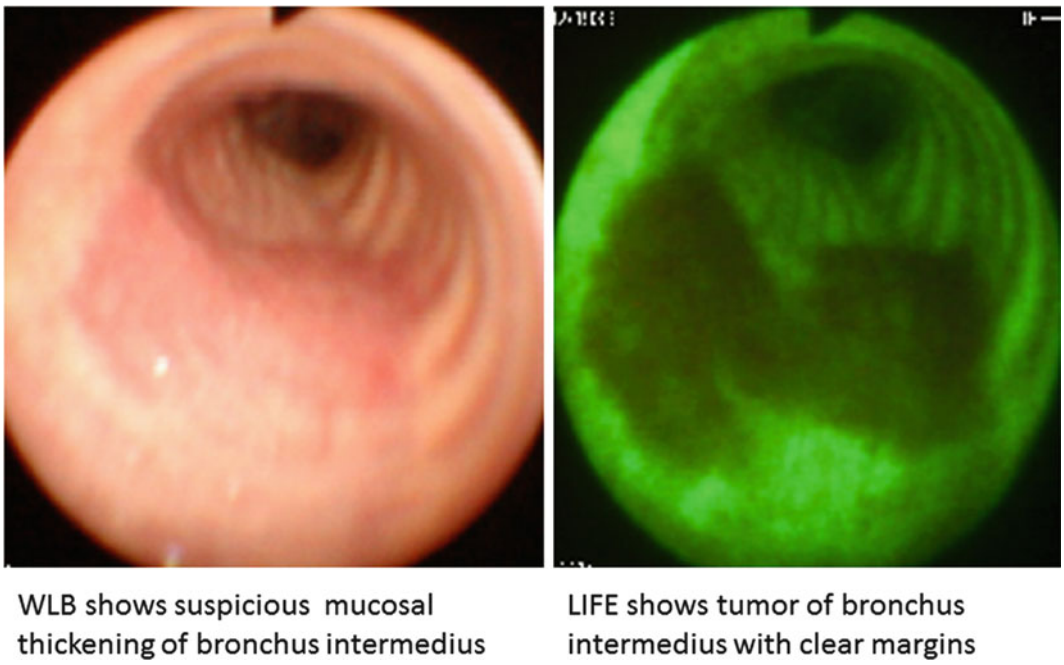

Fig. 21.2 Superficial spreading tumor with margins clearly demarcated by LIFE bronchoscopy

bronchitis or hyperplasia where LIFE would otherwise indicate as abnormal. Although switching from WLB to AFI involves hitting the button on the bronchoscope, simultaneous comparison of the video-endoscopic and AF images cannot be achieved (Fig. 21.2).

Dual real-time display of video-endoscopic and AF images is recently made possible with SAFE 3000 (Pentax, Tokyo, Japan). SAFE 3000 is a video bronchoscope that uses xenon lamp for WLB and allows real-time color image transmission using the miniature charge couple device that is built into its tip. The AF mode utilizes a diode laser that delivers excitation light to the target from the tip of the scope, and fluorescence from the target is captured by filtering out the wavelength of excitation light with the objective lens. Since both light sources are available, dual real-time display of video and AF bronchoscopic images of the target is achieved. Our study showed that dual real-time display of video-bronchoscopic and AFB images was not only sensitive for detecting preneoplastic lesions (0.86), it was highly specific (0.94) as it provided both functional and anatomic information of the lesion simultaneously (Fig. 21.3). By doing so, it allowed targeted biopsy that led to shorter procedural time, better patient comfort, and safety. Good correlation between visual classification (normal, abnormal, suspicious) and pathology was achieved particularly in identifying previous biopsy site, bronchitis, and airway fibrosis following endobronchial therapy (Fig. 21.4).

The newly developed Onco-LIFE device uses both reflectance and fluorescence light for imaging. Blue light (395–445 nm) and small amount of red light (675–720 nm) from a filtered mercury arc lamp are used for illumination. A red-reflectance image together with the green-autofluorescence image is captured by nonimage-intensified

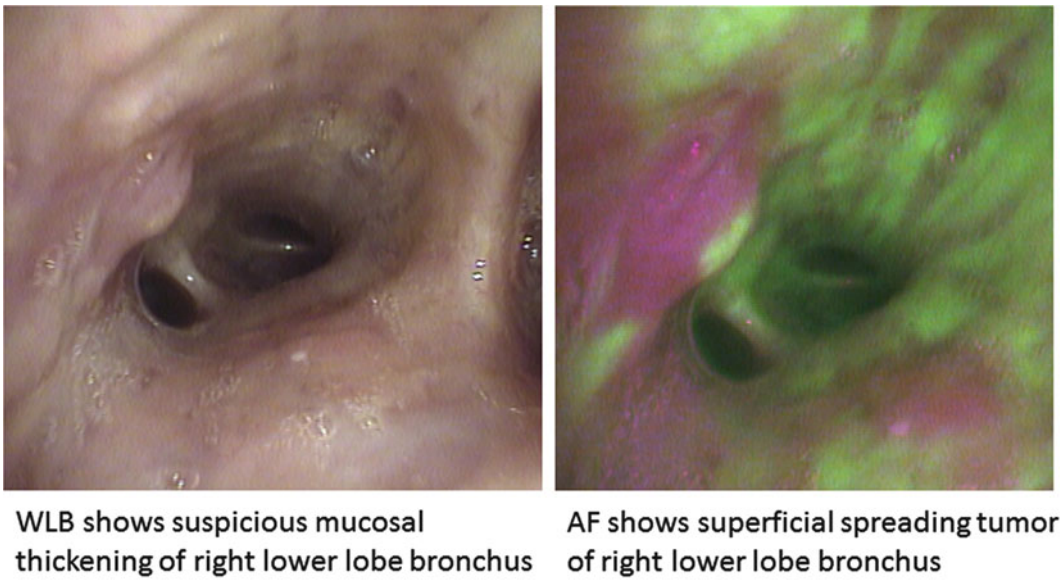

Fig. 21.3 Superficial spreading tumor with margins clearly demarcated by AFI

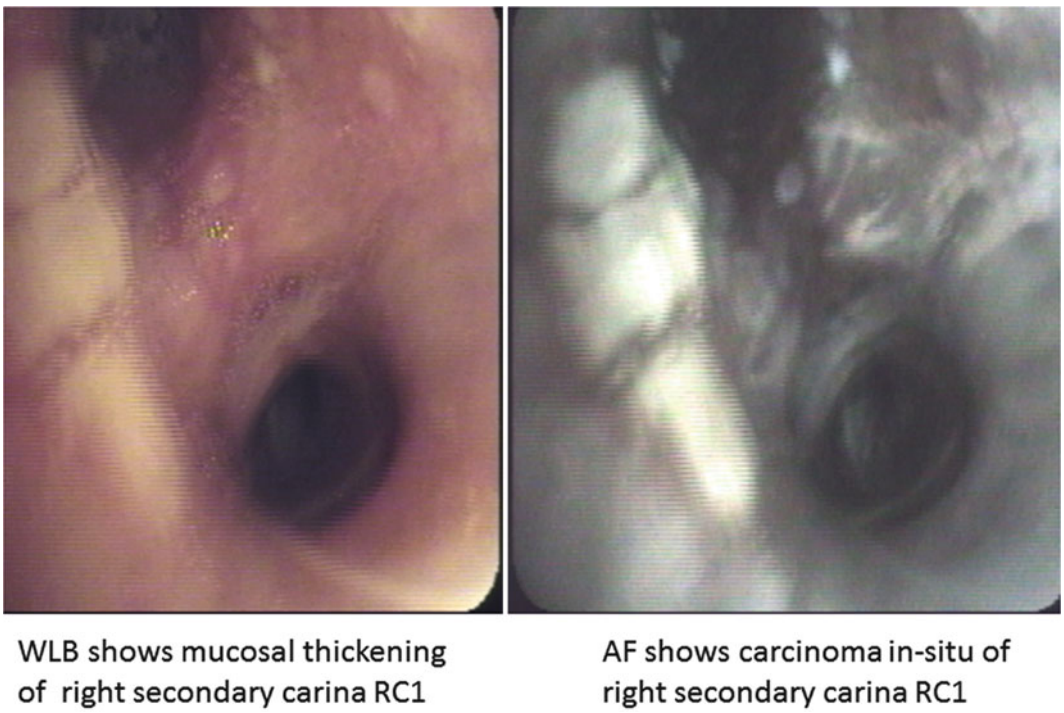

Fig. 21.4 Dual images of carcinoma in situ with SAFE 3000

charge-coupled device which further enhances the contrast between preinvasive/malignant from normal tissues. By using reflected infrared red light as a reference, it has an advantage over reflected blue or green light as it is less absorbed by hemoglobin and may be less influenced by changes in vascularity associated with airway inflammation, thereby reducing its false-positivity. Red light is also uniformly scattered within the tissue and serves as a reference signal from which differences in light intensities due to changes in angle and distance of the bronchoscope from the bronchial surface are corrected (Fig. 21.5). In addition, Onco-LIFE allows quantitative analysis of the fluorescence image by providing a numeric

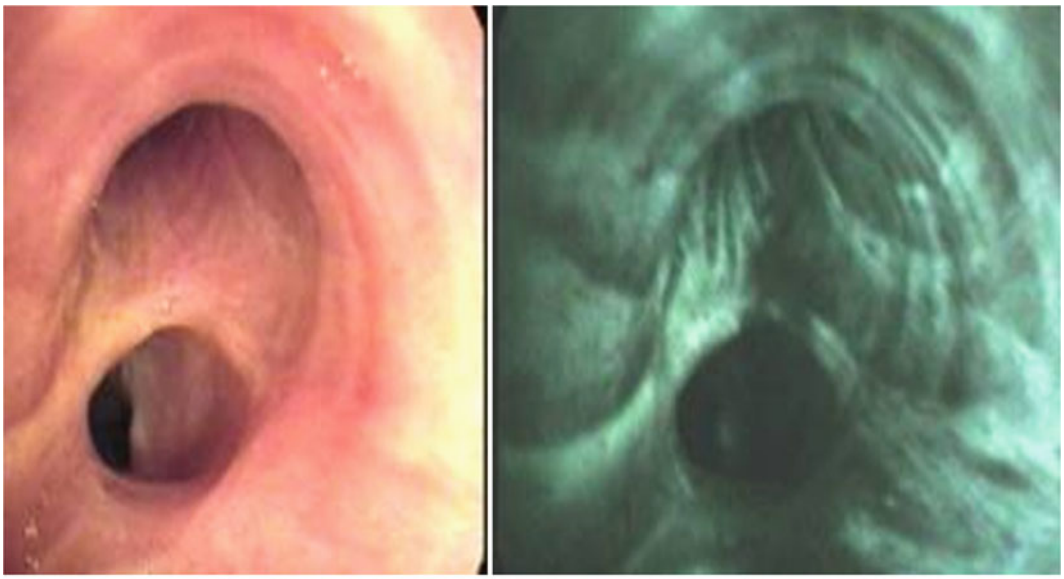

Fig. 21.5 Dual images of previous biopsy site with SAFE 3000

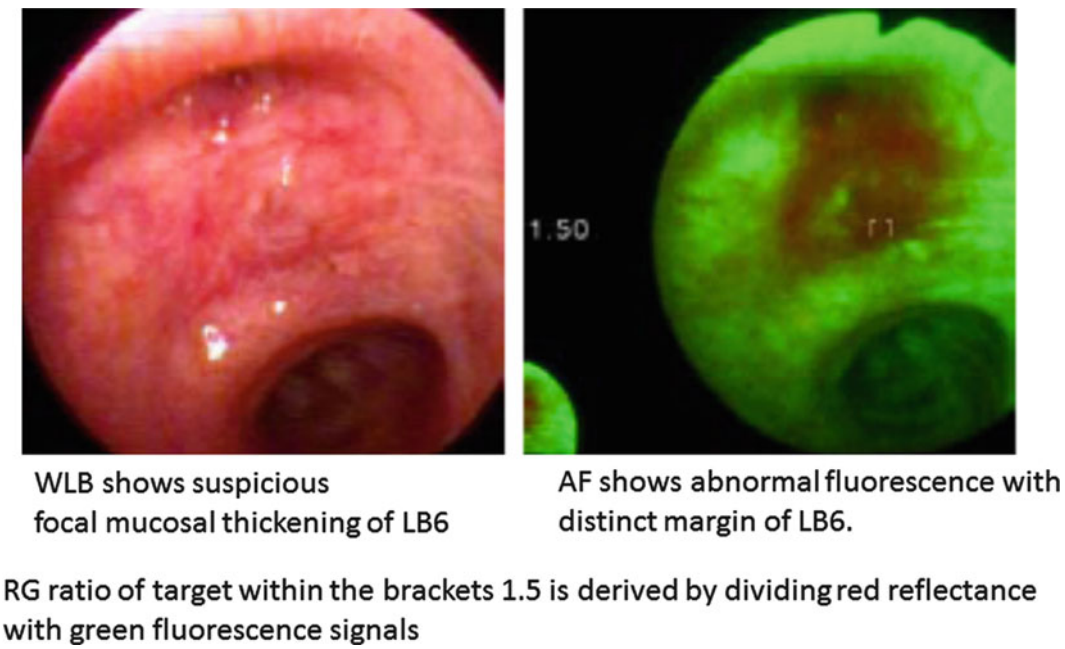

Fig. 21.6 Color fluorescence ratio R/G of carcinoma in situ

representation (R/G ratio) of the combined colors in the central portion of the displayed image. R/G ratio of the 16 × 16 pixel square target defined within the displayed brackets is calculated by dividing the average red reflectance with green fluorescence signals captured by the camera (Fig. 21.6). We performed a study correlating pathology of 3,362 biopsies with their corresponding R/G ratios. R/G ratio 0.54 and greater conferred 85% sensitivity and 80% specificity for the detection of high-grade and moderate dysplasia. When visual score (normal, abnormal, suspicious) was combined with R/G ratio, specificity in diagnosing moderate dysplasia or worse was further improved to 88% suggesting that color fluorescence ratio could objectively guide the bronchoscopist in selecting sites for biopsy with good pathological correlation.

Narrow Band Imaging

The conventional RGB sequential video bronchoscope system has a xenon lamp and rotation disk with three RGB optical filters. The rotation disk and monochrome CCD are synchronized, and three band images are generated sequentially. Color images are created by the video processor. Narrow band imaging (NBI) is a novel system that is developed to enhance microvessel structure using a new narrow banding filter on an RGB sequential video bronchoscope system instead of the conventional RGB broadband filter (Fig. 21.7). Wavelengths used by the NBI filter are B1: 400–430 nm, B2: 420–470 nm, and G: 560–590 nm which are in contrast to the conventional RGB broadband filter, namely, B: 400–500 nm, G: 500–600 nm, and R: 600–700 nm. Tissue optical absorption and scattering properties are wavelength dependent, and blue light has a shorter wavelength that reaches into shallow surfaces. The main chromophore in bronchial tissues is hemoglobin which has a maximum absorptive wavelength near 415 nm within the wavelength range for NBI-B1. Therefore, it is presumed that NBI-B1 filter would detect blood vessel structures more accurately than other filters.

When conventional RGB broadband light is delivered onto tissue surface, light is scattered and absorbed by tissue with little light reflected to form an image; however, if narrow band light is delivered onto same surface, it causes less scattering, thereby enhancing its reflected image. The first publication on NBI combined with high-magnification bronchovideoscopy showed significant association between dotted vessels detected by NBI-B1 and pathological diagnosis of angiogenic squamous dysplasia (ASD) (Fig. 21.8). ASD is a morphological entity of squamous dysplasia of the central airways where collections of capillary blood vessels are projected into dysplastic bronchial epithelium, suggesting that angiogenesis is an early event of lung carcinogenesis. Several studies that investigate into the multistep model of carcinogenesis have indicated that angiogenesis switch occurs in preinvasive lesion prior to invasive tumor development. Although Hirsch and coworkers have demonstrated that fluorescence bronchoscopy was able to detect 75% of ASD cases, AF could not distinguish bronchial squamous dysplasias with ASD from those without. NBI appears to be useful for detecting capillary blood vessels in ASD lesions at sites of abnormal fluorescence. Studies are underway to determine if patients harboring ASD have greater risk for progression to lung cancer. In a pilot study of 22 patients where WLB was performed followed by NBI, NBI identified dysplasia or malignancy not apparent on WLB in 23% of subjects. This was confirmed in a larger trial where 62 patients underwent WLB then randomized to AFI or NBI. The objective was to determine if there was any value combining NBI with AFI and WLB. Respective sensitivities and specificities of AFI and NBI were 3.7/3.0 and 0.5/1.0 relative to WLB. Addition of NBI to AFI did not increase the diagnostic yield significantly, and sequence with which AFI and NBI was performed did not impact findings. The authors proposed NBI as an alternative to AFI for early lung cancer detection since WLB

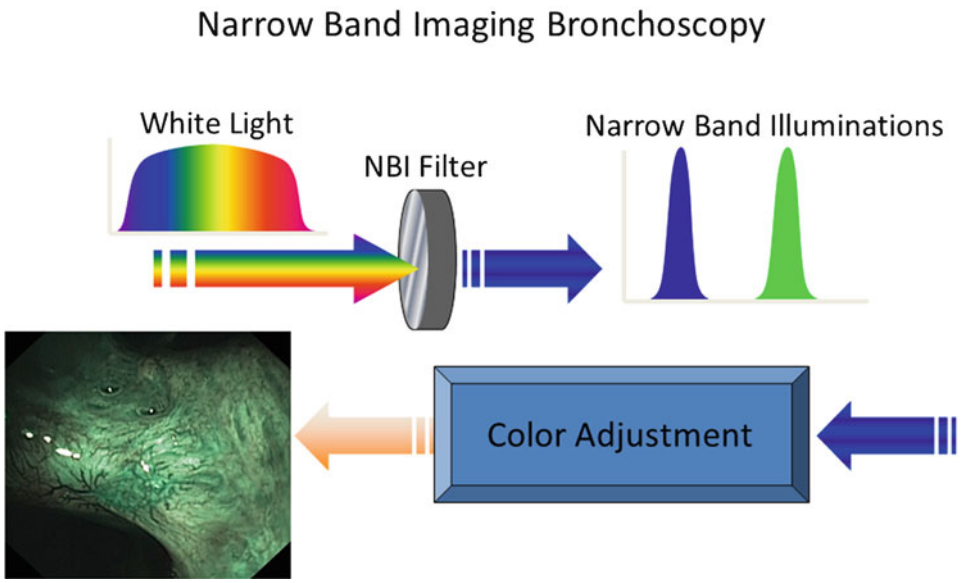

Fig. 21.7 Narrow band imaging enhances microvessel structure by means of narrow banding filter instead of conventional RGB broadband filter

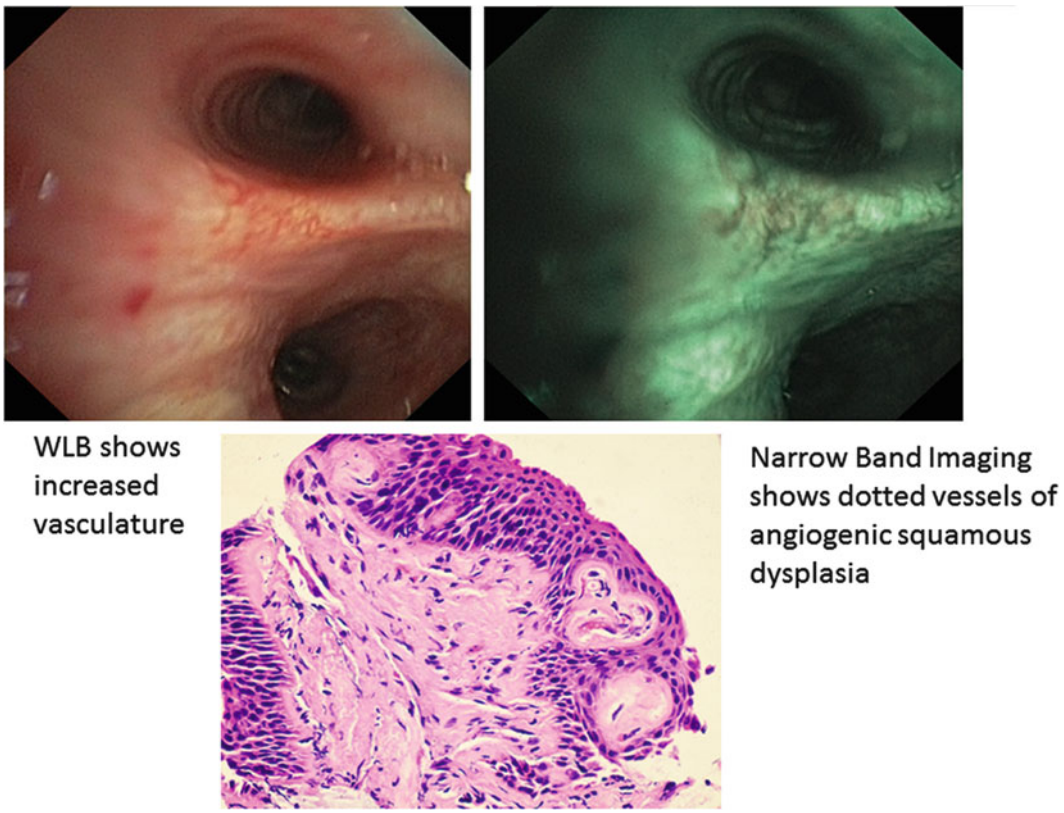

Fig. 21.8 Narrow band imaging shows dotted vessels of angiogenic squamous dysplasia

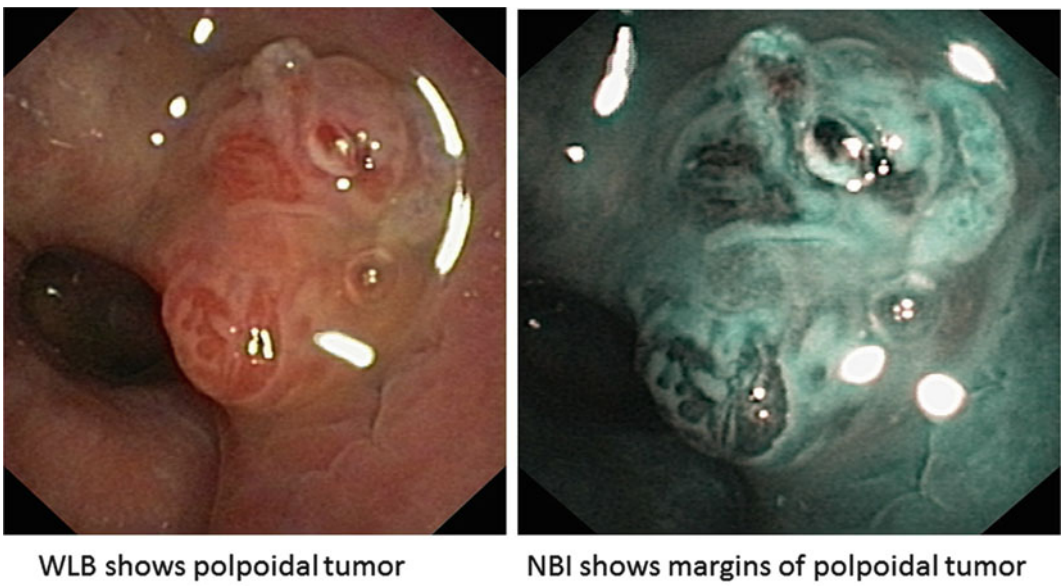

Fig. 21.9 Narrow band imaging shows tumor margins

could be converted to NBI by merely pressing a switch button on available bronchoscopy systems (EVIS EXERA II, BF-Q180/BF-IT180, Olympus Medical Systems Corp., Japan) unlike AFI that required a change of bronchoscope (Evis Lucera video bronchoscope BF-F260, Olympus Medical Systems Corp., Japan). NBI was also found to be useful in early detection of head and neck cancers as well as impacting therapeutic decision in the assessment of tumor extension for centrally located lung cancer (Fig. 21.9).

Clinical Applications

CELC must first be radiographically occult without lymph node and distant metastasis. The squamous cell cancer should measure less than 2 cm in greatest dimension with visible distal margin and located in the subsegmental, proximal bronchi or trachea. CELC is classified into five categories: polypoid, nodular, thickened, invisible, and mixed. Konaka and coworkers have found that tumor dimension strongly correlates with the depth of bronchial invasion. Polypoid or nodular types tend to invade more deeply than the thickened and flat lesions. In fact, polypoid or nodular lesions that measure less than 10 mm and flat lesions 15 mm or less tend to be confined within the cartilaginous layer without nodal metastasis. Thus precise evaluation and staging of CELC are important steps toward treatment selection. Surgery is still the treatment of choice for CELC, but many of these patients suffer from poor cardiopulmonary reserve due to smoking and are therefore unfit for surgery. Moreover, up to 30% of CELC can be multifocal due to field effect, thereby propelling lung sparing techniques such as photodynamic therapy (PDT) or locally applied bronchoscopic treatment such as endobronchial electrosurgery, cryotherapy, and brachytherapy as attractive alternative options for CELC, in a select group of patients with tobacco-related comorbidities. However, these lesions must be confined within the cartilaginous layer of the bronchial wall, and an ideal lesion for bronchoscopic treatment represents one that is flat and measures 10 mm or less with visible distal margin.

Radial endobronchial ultrasound allows visualization of layered structure of the bronchial wall and can be a good tool in determining peribronchial tumor invasion. Herth and coworkers compared depth of tumor invasion using EBUS and high-resolution CT with pathology of resected lungs in 105 patients with CELC. All CELC with EBUS evidence of tumor invasion were confirmed on pathology. EBUS underestimated tumor invasion in six patients, thereby achieving 89% sensitivity and 100% specificity for invasive cancer. Studies incorporating EBUS as part of staging report complete response with PDT if intracartilaginous CELC are treated.

Optical coherence tomography (OCT) is similar to EBUS but uses light instead of acoustic waves. In ultrasound, imaging is made possible by measuring the delay time (echo delay) for the ultrasonic pulse to be reflected back from tissue, and because velocity of sound is relatively slow, echo delay can be measured electronically. Since OCT uses light which travels 200,000 times faster than the speed of sound, low-coherence interferometry is used. OCT is able to obtain high-resolution, cross-sectional microimages of tissue which can potentially permit optical biopsy in place of conventional excisional biopsy in the future (Fig. 21.10).

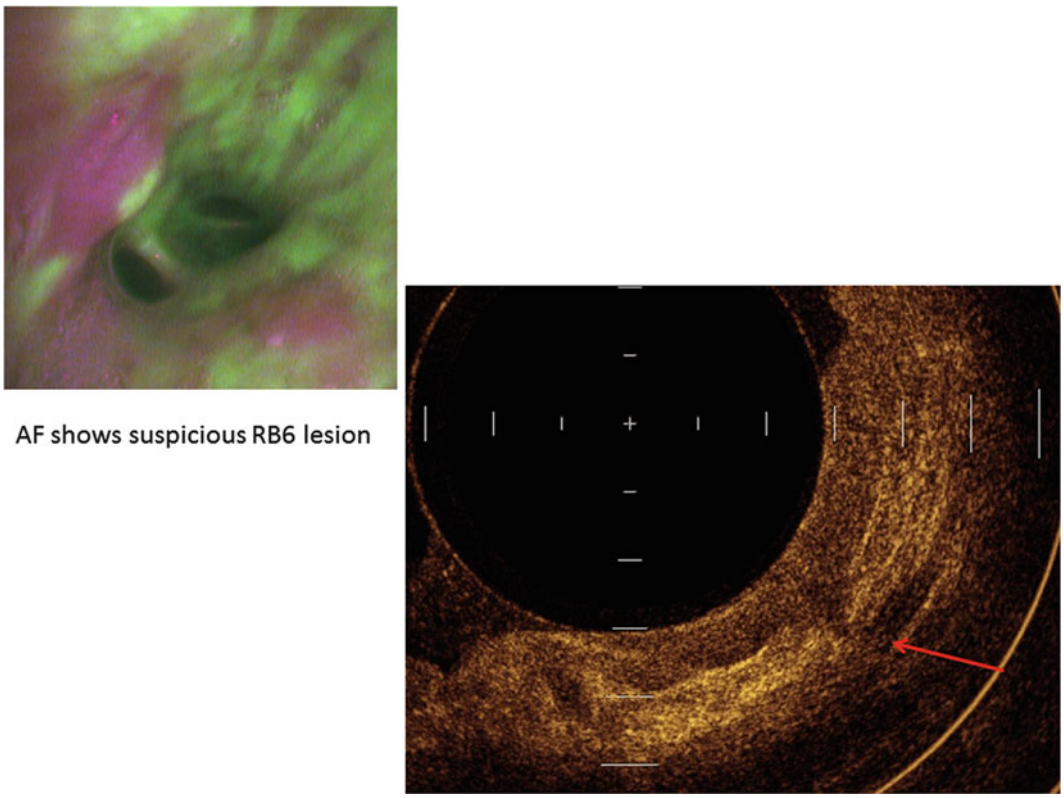

Fig. 21.10 OCT shows microinvasive carcinoma with invasion beyond cartilaginous layer (*red arrow*)

Future Directions

Invasive squamous cell carcinoma of the central airways is believed to develop through a stepwise process where the epithelium changes from normal to hyperplasia; metaplasia; mild, moderate, and severe dysplasia; and CIS. Squamous dysplasia and CIS are categorized as preinvasive lesions by the recent WHO histological classification. The stepwise model is supported by serial sputum cytological examinations from uranium miners and smokers which show progression from mild, moderate, and severe atypia through CIS to invasive cancer. However, sputum can come from different parts of the tracheobronchial tree and sputum atypia leading to cancer may reflect field cancerization rather than evolution within the same lesion, and the concept of stepwise progression of preinvasive lesions to invasive carcinoma is recently challenged. In attempt to clarify the natural history of preinvasive lesions, longitudinal studies using serial AF and biopsy were performed. About 59% of severe dysplasia regressed spontaneously, while 41% persisted or progressed to CIS or invasive cancer. Majority of CIS progressed to invasive cancer within a median of 30 months, recurred despite bronchoscopic treatment, or persisted. George and coworkers followed patients with severe dysplasia or CIS, and they found that five patients with six CIS lesions progressed to invasive cancer within 15 months, of which three patients had progressive disease despite radical therapy or PDT. The authors concluded that since majority of CIS progressed and could become incurable by local therapy, treatment was preferable instead of surveillance with repeat AF and biopsies. Spontaneous regression is more common for mild/moderate dysplasia; Hoshino and coworkers found only 1 of 88 low-grade dysplasia progressed to invasive carcinoma. In another study, none of low-grade dysplastic lesions progressed to CIS or invasive cancer over 12–85-month follow-up. Therefore, a major hurdle in any early lung cancer detection program is to select with accuracy airway lesions that are at high risk of progression to invasive cancer for treatment, and genomic changes responsible for malignant bronchial transformation such as inactivation of tumor suppressor genes, activation of oncogenes, loss of heterozygosity (LOH), and amplifications of chromosomes have been detected in preinvasive lesions by microdissection techniques. By analyzing genomic patterns in preinvasive lesions (moderate dysplasia to CIS) using fluorescent in situ hybridization (FISH), four probes (TP63, MYC, CEP3, and CEP6) tend to correlate with progression to invasive cancer with 85% sensitivity and 58% specificity. Loss of heterozygosity of 3p allele is also strongly associated with endobronchial-treatment-resistant CIS and severe dysplastic lesions and those that progress to invasive cancer despite therapy. Overexpression of p53, cyclin D1/cyclin E, and Ki-67 detected by immunohistochemistry increases according to histological grade of bronchial dysplasia, and microRNA expression profiling seems to be highly predictive of the histological grade of preinvasive lesions identified by AF. Recognizing characteristic trends of expression can lead to early diagnosis of lung cancer. Thus, it is apparent from emerging data that molecular analysis can not only aid in more precise histopathologic grading of preinvasive lesions but its incorporation into a molecular-based management decision tree may also allow the clinician to identify and target treatment with precision on airway lesions that harbor characteristic molecular signatures which signify high risk of progression to invasive lung cancer.

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Confocal Imaging

22

Devanand Anantham

Introduction

Alveolar and bronchial biopsies obtained via flexible bronchoscopy are the most common lung tissue specimens submitted to pathologists worldwide. Surgical sampling has complications associated with general anesthesia while computed tomography (CT)–guided biopsies run the risk of pneumothorax. These complications, coupled with the safety and availability of flexible bronchoscopy, have contributed to the widespread acceptance of bronchoscopic biopsies. However, transbronchial lung biopsies remain relatively blind procedures guided only by pre-endoscopy imaging until the recent advent of navigational systems and radial endobronchial ultrasound. Pneumothorax and bleeding rates of 1–3% are typically reported. Although well tolerated by the majority of patients, these risks can be significant to those with preexisting cardiopulmonary compromise. Specimens obtained by forceps biopsies are also subject to crush artifact. The biopsied regions often undergo scarring, and the natural history of disease can be altered. Processing of tissues involves dehydration and chemical fixation that result in specimens not being analyzed in their natural state. The risks of bronchoscopic biopsy and the limitations of specimen handling have fueled the development of optical in vivo biopsies. Ideally, real-time images of histopathological quality can be obtained that will facilitate a noninvasive diagnosis. This will also enable monitoring of both treatment response as well as natural progression of disease with minimal complications. Pathology such as diffuse interstitial lung disease where the risk of biopsy is particularly high or conditions where multiple biopsies are needed longitudinally such as lung transplant follow-up and early lung cancer screening are likely to benefit from such advances most. One technology leading the pursuit of such optical biopsies is confocal microscopy.

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Principle of Probe-Based Confocal Microscopy

Confocal microscopy is based on both point-source illumination and pinhole light detection (Fig. 22.1). In conventional microscopy, light from objects that are above and below a focal plane interferes with and blurs the image produced. In confocal imaging, a pinhole obtains fine optical sectioning with cellular level resolution by rejecting out-of-focus data beyond a thin focal plane. However, this resolution is achieved at the cost of decreased light signal intensity that is received by the photodetector. The decreased intensity needs to be compensated for by prolonging exposure time. The "confocal" terminology refers to a system where the illumination and detection systems are located on the same plane.

Confocal microscopy that was initially used in gastroenterology utilized a miniaturized scan head located on the distal end of the endoscope. Such scopes need to be stabilized to obtain distinct images that are free of motion artifacts because of a slow scan rate of 1 frame per second. A prototype for pulmonary application with such a distal scan head has an external diameter of 6.6 mm, requires rigid bronchoscopy for airway insertion, and visualizes only the central airways. Distal airway imaging is precluded by the size of the scope. White-light bronchoscopy is also unavailable in this prototype. The advantage of the distal scan head is that it allows adjustment of depth of focus (z-depth) and facilitates imaging of epithelium down to submucosal vasculature (200 μm). Much of the current experience with pulmonary confocal microscopy has been with a proximal scanning system that houses the light source and photodetectors outside the bronchoscope. A miniprobe comprising optical fibers is inserted via the working channel of a flexible bronchoscope to transmit signals to and from the probe to the proximal scanning unit. These miniprobes have faster scan rates of 12 frames

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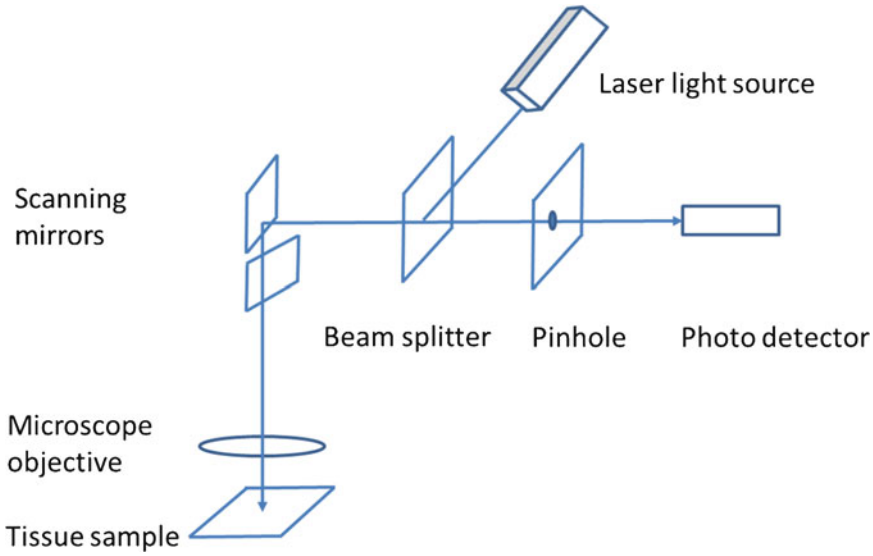

Fig. 22.1 Principle of confocal microscopy using point illumination and pinhole detection

per second that reduce motion artifacts. The disadvantage of the proximal, fiber-based system is that focal point of the microscope cannot be adjusted. Therefore, the z-depth is fixed at 50 μm below the contact surface.

The fiber-based confocal microscopy system (Mauna Kea Technologies, Paris, France) that is currently available comprises four components: (1) the flexible miniprobe, (2) argon-laser illumination source with an excitation wavelength of 488 nm, (3) monopixel photodetection system, and (4) image management software (Fig. 22.2). The miniprobe has an outer diameter of 1.4 mm and a length of 3 m. This makes the probes compatible with the working channel of standard flexible bronchoscopes. There are 30,000 optic fibers arranged in a hexagonal pattern that serve as a link between the microscope objective and the proximal scanning unit. The core diameter of each fiber is 1.9 μm with an intercore distance of 3.3 μm. The resultant images comprise 30,000 pixels in a field of view of 600 by 500 μm with a lateral resolution of 3.5 μm.

Each fiber serves as both the light delivery system and its own pinhole. These fibers are scanned sequentially by the laser, and in order to generate a two-dimensional image, the sample is scanned in both lateral dimensions. This is achieved by two rapidly moving (4 Hz) mirrors that scan across the fiber bundle in a raster or grid-like fashion (Fig. 22.1). The photodetection bandwidth ranges from 500 to 650 nm in wavelength. The numerical aperture of the objective lens coupled with this photodetection bandwidth and the optical properties of certain tissue also enable profiling of surfaces with three-dimensional images. Numerical aperture refers to the range of angles over which a system emits or accepts light.

Fig. 22.2 Fiber-based, proximal confocal microscopy system with an *arrow* indicating the miniprobe that is inserted via the working channel of a flexible bronchoscope

Each fiber samples only a single point on the tissue, and image processing builds a mapping based on all these point sources of data. Stored data can later be reviewed using viewer software to make measurements. Fluorescence intensity as measured by the median pixel intensity over a selected image area can also be calculated. Further processing of video sequences is possible with a mosaicing algorithm that recovers a consistent alignment of input frames and utilizes data-fitting to "stitch" together a mosaic. This algorithm combines successive images, as well as cancels movement-induced artifacts before reconstituting a larger static image with a widened field of view. The image area is then increased two- to fourfold. This mosaic processing provides endoscopists with a more complete representation of the targeted region that can be comparable to standard histopathology.

The current limitation of mosaicing is that it is performed post procedure and provides neither real-time information nor direct feedback to the operator on the quality of image acquisition. Dynamic processes such as respiratory motion and blood flow are also not captured. In imaging the lung periphery, miniprobe manipulation is restrained by the size of distal airways, and acquisition of a larger field of view is possible in only half of all bronchopulmonary segments examined. Mosaic stitching of images may be further limited when alveolar fluorescence is reduced, for example, in young individuals with faint septal lines. The reduced fluorescence diminishes signal data available for mosaic "stitching." In proximal airways, even when miniprobe manipulation is not restrained, the smooth scanning required to generate mosaics is challenging with respiratory movements and coughing. Good imaging also requires perpendicular en-face scanning of the airway walls that can pose ergonomic difficulties.

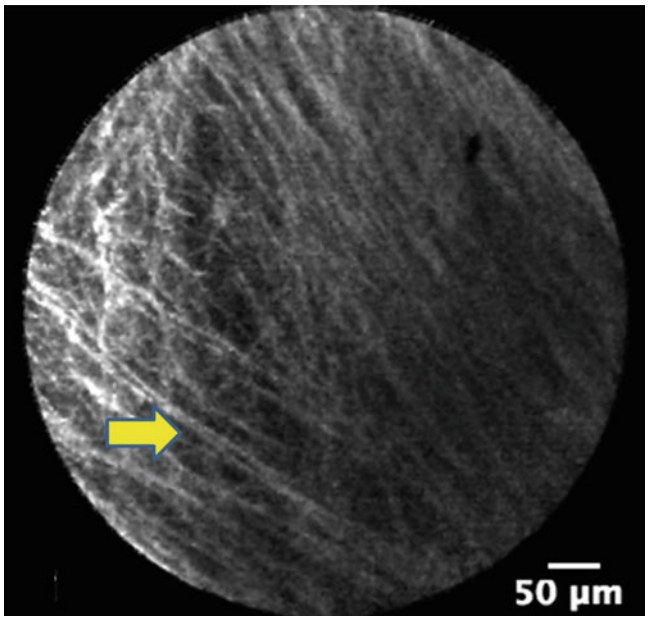

Fig. 22.3 Elastin fibers (*arrow*) of the basement membrane of bronchi

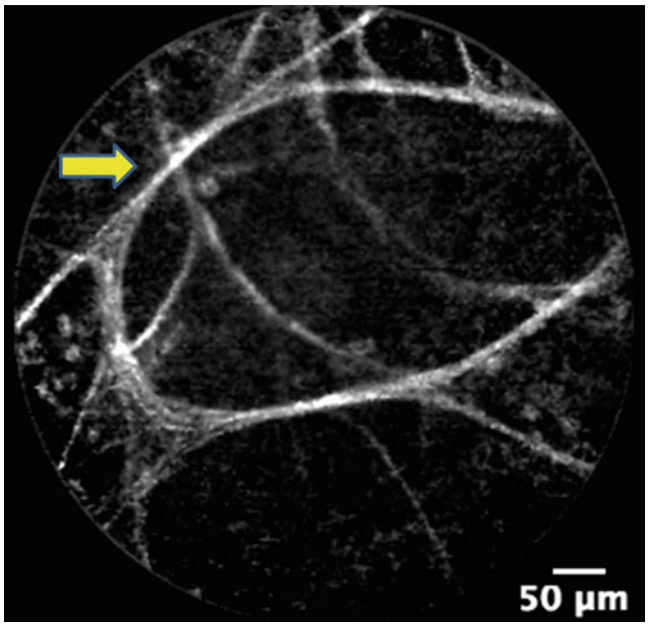

Fig. 22.4 Elastin fibers (*arrow*) of the axial scaffolding of pulmonary acini

Image Acquisition in the Lungs

Imaging depends on the fluorescence of the targeted tissue which in turn is determined by the concentration of endogenous cellular and extracellular fluorophores. The predominant fluorescence emission in the lungs after excitation with light at 488 nm originates from elastin as demonstrated by microspectrometer data. On the other hand, collagen and intracellular flavins do not contribute to imaging because they emit an extremely weak signal. Elastin is a major component of the basement membrane of the airways (Fig. 22.3) and the axial scaffolding of pulmonary acini (Fig. 22.4). These fibers function to bear the stress of airway distension and facilitate lung recoil. They are concentrated at the alveolar duct rims, as well as the alveolar ring entrances. Elastin is also part of the external sheath of microvessels in the lung parenchyma. The intensity of elastin fluorescence increases with age, presumably related to cross-linking modifications that occur with time. Sometimes bright specks that are about 3 µm in size are also seen in the alveoli. The cause and significance of this finding has yet to be established.

Endogenous fluorescence is seen in the cells that infiltrate the alveoli of smokers (Fig. 22.5). Bronchoalveolar lavage analysis has confirmed that these cells are alveolar macrophages. The number, size, and mobility of these fluorescent

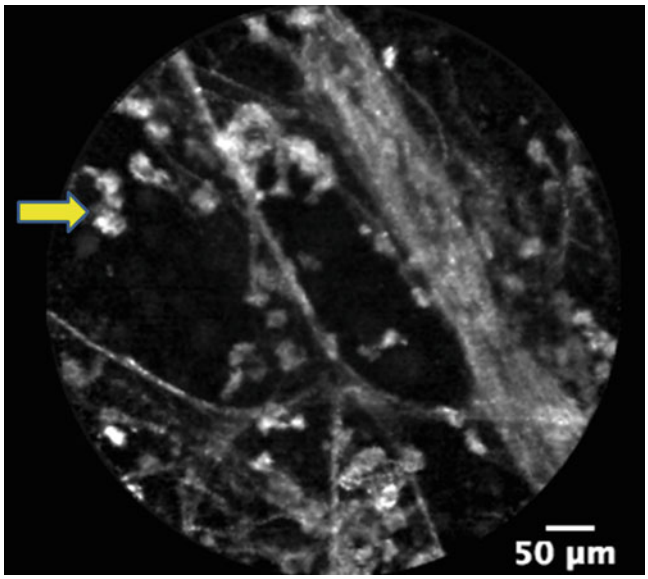

Fig. 22.5 Mobile, fluorescent macrophages (*arrow*) in the alveoli of a current smoker

macrophages are directly correlated to the number of cigarettes smoked per day reflecting the degree of macrophage alveolitis. In vitro evidence shows that the fluorescence is attributed to the particulate fraction of cigarette smoke especially tobacco tar. There is similar data using exposure to oil fly ash to explain why nonsmokers have a dim, less distinct macrophage fluorescence caused by the inhalation of air pollution.

Exogenous fluorophores that are not toxic have been utilized to enhance imaging on confocal microscopy. Intravenous agents such as fluorescein as well as topical agents such as cresyl violet or methylene blue have shown potential in this area. The use of intravenous fluorescein as a contrast agent has been established in ophthalmology for more than 30 years and has FDA approval for such indications. Although it does not stain nuclear structures, in confocal microscopy of the gastrointestinal tract, fluorescein enhances the imaging of epithelial cells. The peak excitation is with light of 494 nm in wavelength that makes it compatible with the current laser source. The quick diffusion of fluorescein will allow images to be seen 30 s after injection and effects last up to 30 min with an optimal image quality at 8–10 min. This is compatible with bronchoscopic procedures. Typically, 10 ml of 0.25% fluorescein sodium solution is injected via a peripheral venous catheter, and bronchoscopic evaluation is performed 1 min after injection. Side effects include nausea and vomiting that are reported in 2.2% as well as temporary yellow discoloration of the eyes and skin. Rare adverse events include anaphylaxis, seizures, thrombophlebitis, and arterial ischemia. Fluorescein should be used with caution in patients on β-blockers because of the risk of anaphylaxis as well as anyone with renal dysfunction or a recent ischemic cardiac event.

Fluorescein-enhanced confocal microscopy of normal alveoli clearly reveals a foam-like picture with the identification of dark air bubbles. It is hypothesized that the air-liquid interface at the tip of the miniprobe creates these bubble-like structures that can also be seen faintly in imaging unenhanced by fluorescein. What is uncertain is whether this fluid is only surfactant or airway secretions that have been brought in during the placement of the miniprobe. Fluorescein is secreted in large amounts into the intrapulmonary fluid of distal airways and enhances the bubble foam that is superimposed on imaging of alveoli. In malignant and inflammatory disease, cellular infiltration appears to remove surfactant and obliterate the formation of bubble foam. Instead images of dark cell-like structures may be seen adjacent to alveolar walls.

In the proximal airways, fluorescein disappointingly does not stain epithelial cells and consequently does not aid imaging. Even when large endobronchial lesions were directly imaged with the miniprobe, tumor cells were not seen. This is in direct contrast to gastrointestinal imaging where fluorescein enhances the epithelium. A differential absorption of the stain by mucosa in the respiratory tract compared to the gastrointestinal tract is suggested, possibly secondary to differential perfusion. Another reason for the poor results with fluorescein in the bronchi is the fact that miniprobes used for the gastrointestinal tract utilize light at a wavelength of 660 nm and consequently have a different focal plane.

Methylene blue is a potent topical fluorophore that enters cells and reversibly binds with DNA in the nuclei. However, the maximum excitation is with light of wavelength 664 nm which necessitates the use of the 660-nm miniprobe. When used in clinical practice, the targeted airways are initially scanned with the pulmonary 488-nm probe before topical instillation of 0.5 ml of diluted methylene blue and rescanning with the 660-nm gastrointestinal miniprobe. In the proximal airways, it has been possible to image the epithelial surface of the bronchi. If peripheral lung lesions are targeted, then methylene blue is instilled via an extended working channel, and cellular details of tumor cells in lung nodules can be seen. Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because of the risk of oxidative stress-induced hemolysis. Physiological pH cresyl violet (excitation maximum at 591 nm and emission maximum at 628 nm) is being developed as another topical fluorophore. It is an organic compound that is used as a common stain in white-light microscopy. The advantage of this stain is that the 488-nm excitation light can be utilized, making any change of miniprobe unnecessary.

Clinical Potential of Confocal Imaging

Probe-based confocal imaging is usually performed using flexible bronchoscopy necessitating only moderate sedation. The tiny field of view makes systematic examination of the entire airways impractical. Therefore, white-light bronchoscopic examination is first performed before an area of interest is scanned with the microscope. Optical biopsy images are obtained by perpendicular application of the probe directly against the bronchi. A mosaic is then created by gently drawing the probe across the target. To obtain optimal images, secretions must be suctioned out and the airways adequately anesthetized with topical lidocaine.

Examination of distal bronchopulmonary segments is ideally performed with a small bronchoscope (outer diameter 4.4 mm) to facilitate navigation in the smaller bronchi. Usually up to eight segments are scanned based on preprocedure CT analysis, and only unilateral examination is performed because of the potential for pneumothorax. For subsequent correlation with radiology, rigorous documentation of which segment that is entered is necessary. Scanning of the apical and posterior segment of the upper lobes is not possible because of the inherent stiffness of the miniprobe.

Once the bronchoscope is placed in the smallest accessible bronchus, the miniprobe is gently advanced until images of the pulmonary acini are seen. The orthogonal branching of the airways and the size of the probe relative to distal airspaces presume that the probe passes through bronchiolar walls and peribronchial connective tissue before being stabilized in the acini. Hence, respiratory bronchioles are regularly bypassed in scanning. Typically, en-face images are obtained, but images at various angles providing various perspectives can be seen as well. Once the alveoli are reached, there is a compression effect that is caused by the probe pressing on more distal structures. This visualizes the background planes that are beyond the 50-μm focus, creating a three-dimensional effect. Best results are obtained by withdrawing the probe once acini are seen and analyzing the last image before contact is lost (Fig. 22.4). At this point, deformation is minimized and reproducible measurement of alveolar structures is possible.

In practice, video segments of confocal scanning of up to 30 s are recorded in each segment once clear and consistent images are seen. Then, mosaic images are stitched together, and representative still pictures are obtained. The viewer software facilitates measurement of both structure dimensions and fluorescence intensity. Intraobserver and intrapatient reliability have been proven to be excellent. Interobserver agreement between blinded reviewers on the brightness of images has been shown to be high with an intraclass correlation coefficient (ICC) ranging from 0.53 to 0.99 ($p < 0.001$). However, the agreement on fiber thickness in the respiratory bronchioles is poor with an ICC of 0.12 ($p < 0.05$) and in the alveoli is fair with an ICC of 0.37–0.42 ($p < 0.001$). Software image interpretation has shown excellent correlation with endoscopists' interpretation with an ICC of 0.62–0.99 ($p < 0.001$).

Patients tolerate confocal microscopy well with alveolar imaging requiring a mean of 11 ± 5 min. It has been performed safely on patients with interstitial lung disease, severe emphysema, and post-lung transplantation. Safety data in critically ill, ventilated patients is currently being sought. Although, the procedure is only performed unilaterally and post procedure chest radiographs are routine, pneumothorax as a complication of confocal microscopy is rare with only a single isolated report. Trauma to the proximal airways is not encountered, but mild bleeding may occur in imaging the pulmonary acini. This is attributed to probe-induced rupture of microvessels. Patients are usually asymptomatic except for transient pleurisy that is felt on reaching the visceral pleura. The absence of pain receptors in the bronchial tree makes penetration of bronchiolar walls by the miniprobe during distal airway scanning completely painless. Although no data exist in the pulmonary literature, a study on the learning curve of gastrointestinal confocal scanning shows that new endoscopists are able to obtain reasonable images almost immediately. Interpretation of these images is more challenging with an accuracy of 63% over the first 20 lesions that rises to 86% when 60 lesions are reviewed.

Imaging of Bronchial Walls

The focal depth of confocal microscopy results in imaging beyond the epithelial contact surface, and instead the basement membrane zone is seen. This zone includes the lamina densa and lamina reticularis (Fig. 22.6). A mat of large, longitudinally orientated fibers are seen cross-linking with finer fibers (Fig. 22.7). This suggests that the subepithelial layer consists of at least two superimposed sheets of elastin that are perpendicularly orientated. In normal individuals, Thiberville et al. have described five patterns depending on the location within the bronchial tree.

1. At the main carina, mainstem bronchi, and anterior wall of the trachea, a dense homogenous pattern without crossing fibers is seen.
2. At the subcarinal orifices of the lobar bronchi, a network of tightly compacted and crossing fibers is found. This pattern is also seen around bronchial gland openings which are 100–200 μm in diameter (Fig. 22.8).
3. The rest of the bronchi have the classical mat pattern of longitudinal 10-μm fibers that are crossed perpendicularly by thin fibers (Fig. 22.7).
4. At the bronchiolar level, an interlacing lattice of 2–5-μm fibers is found (Fig. 22.3).

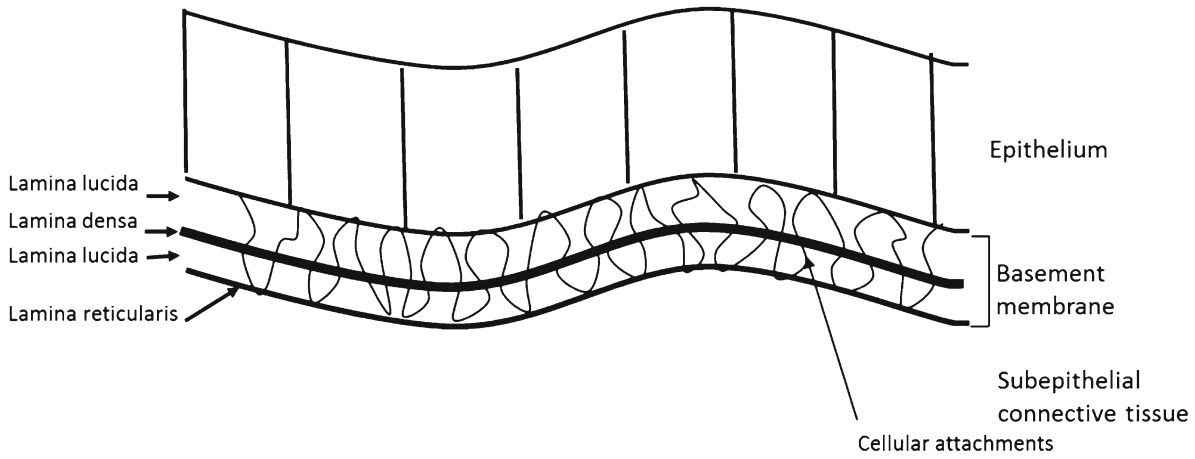

Fig. 22.6 Basement membrane layers of the bronchial epithelium

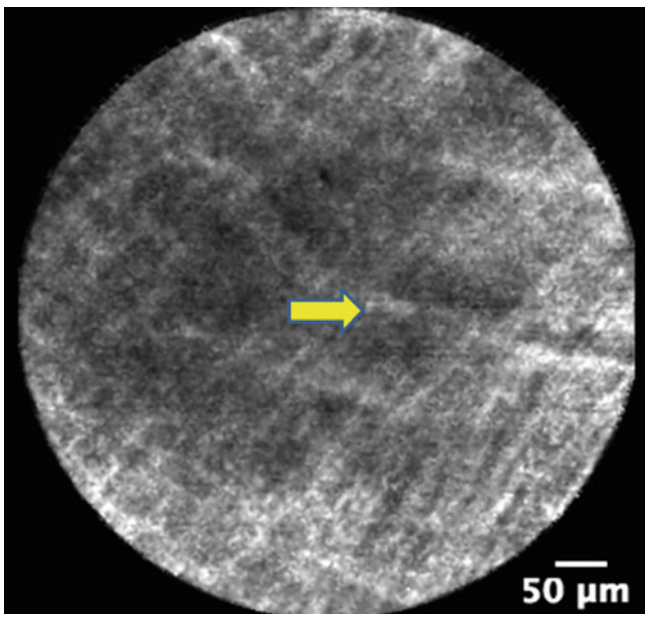

Fig. 22.7 Longitudinal 10-µm fibers (*arrow*) that are crossed perpendicularly by thin fibers

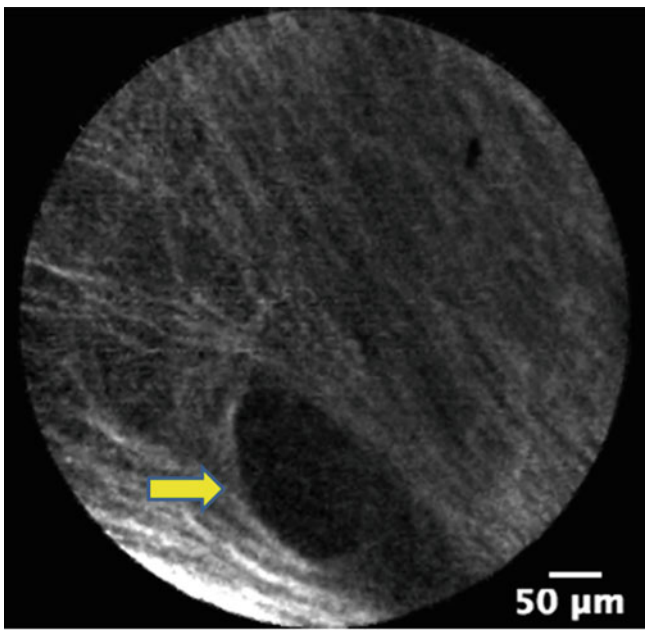

Fig. 22.8 Network of tightly compacted and crossing fibers around bronchial gland opening (*arrow*)

5. Terminal bronchioles are identified by a helicoidal pattern from the organization of smooth muscles and axial connective tissue.

This understanding of bronchial basement membrane imaging has potential clinical applications especially in the detection of early lung cancer. Carcinoma in situ and severe dysplasia cause the regular fibers of airways to appear disorganized or not be seen altogether. In vitro studies have shown that such preinvasive lesions are associated with the early remodeling of the basement membrane through proteolytic degradation. These changes also explain the loss of signal in autofluorescence bronchoscopy that has been traditionally studied in lung cancer screening. Follow-up bronchoscopic screening every 3–6 months has been recommended for high-grade dysplasia and immediate treatment advised for carcinoma in situ. Both guidelines offer further applications because confocal microscopy can be utilized to avoid repeat biopsy in the follow-up of high-grade dysplasia. It can also help define the outer edges of lesions prior to endoscopic or surgical therapy. However, there is currently no proven method to reliably image the epithelial layer with confocal microscopy, and so this technology has yet to be able to distinguish the different grades of squamous dysplasia.

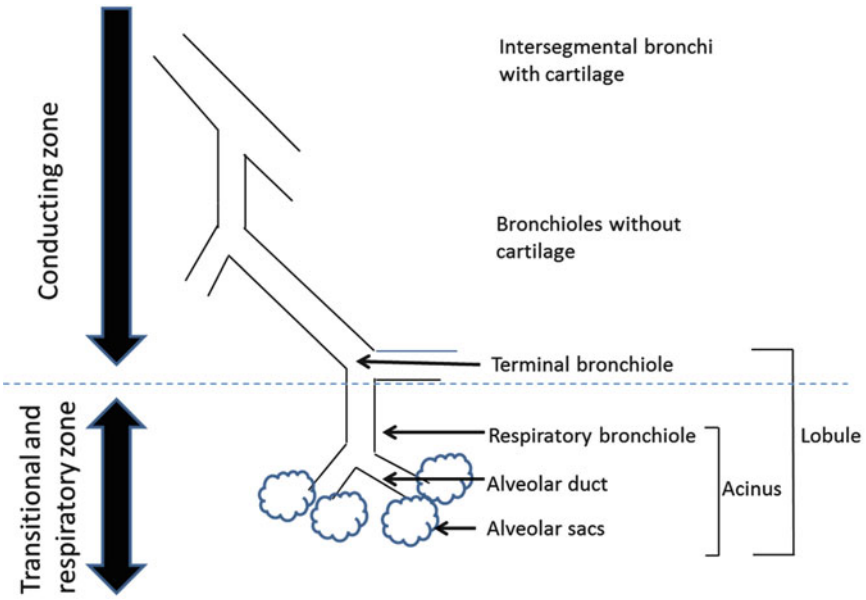

Fig. 22.9 Subdivisions of the intrapulmonary airways

Nonmalignant airway lesions are also currently being mapped out. In Mounier-Kuhn syndrome or tracheobronchomegaly, there is an absence of the network of fibers in airway walls. This is explained by atrophy of elastic fibers, as well as muscular thinning in the trachea and bronchi that is characteristic of this syndrome. In endobronchial sarcoidosis, nodular, nondistinct lesions are seen that corresponded to the classical finding of subepithelial, noncaseating granulomas. This is explained by tropoelastin gene expression in granulomatous lung disease that leads to elastin accumulation. Optical biopsies of tracheobronchial amyloidosis have a fluorescent, "cotton wool" appearance with disruption of the normal basement membrane network. This is attributed to the accumulation of naturally autofluorescent amyloid plaques in the mucosa and submucosa. Confocal microscopy has been able to identify such amyloid plaques even in parts of the airways that appear macroscopically normal on white-light bronchoscopy. This suggests that there may be a role for this technology in preclinical diagnosis. Furthermore, airway inflammation in asthma and chronic obstructive pulmonary disease is currently being studied.

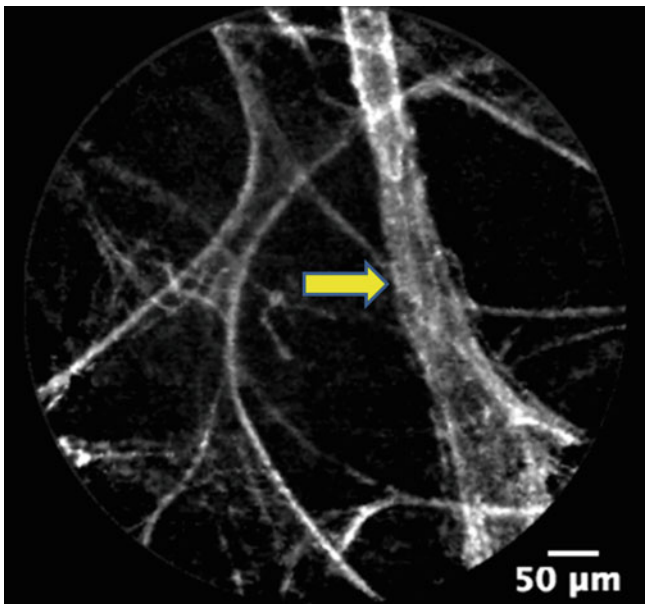

Fig. 22.10 Microvessel (*arrow*) in the lung parenchyma

Imaging of Distal Airspaces

Confocal microscopy can reproducibly image the axial framework of the alveolar ducts (Fig. 22.9), as shown by data from Thiberville et al. Although alveolar entrance diameters are normally distributed with a mean size of 278 ± 53 µm, they appear smaller in the upper lobes and right medial basal segment (paracardiac region). This may be related to the reduced ventilation in these bronchopulmonary segments in the supine position. The mean axial fiber thickness in healthy individuals is 10 ± 2.7 µm with no measured differences between smokers and nonsmokers. Microvessels are distributed throughout the lung with a mean diameter of 90 ± 50 µm (Fig. 22.10). Image interpretation depends on the angle of entry into the alveoli. A helicoidal or cylindrical pattern of rings is seen if the miniprobe enters directly down the axis of alveolar duct. On compression with the probe, deeper planes of views can be seen without any distortion of the first focal plane. A helical configuration is seen if the alveoli are entered obliquely, and a ladder-stitch pattern that elongates longitudinally with respiration is identified when entered laterally.

Minor trauma can be expected given the relative size of the miniprobe compared to distal airspaces. Therefore, terminal bronchioles are often bypassed, and free-swaying septal walls as well as traumatic severing of microvessels can be encountered.

Smokers differ from nonsmokers by the presence of mobile, fluorescent macrophages (Fig. 22.5). This macrophage alveolitis is found in more than 90% of alveoli explored in smokers and less than 1% of nonsmokers. These fluorescent cells can provide contrast that illuminates further details such as capillary networks and alveolar recesses that may be pores of Kohn (interalveolar connections).

Quantitative and qualitative variations in the elastin fibers are being exploited to distinguish pathology from normal. In severe emphysema, dark holes are seen in the acini with a reduction in number of septa. This corresponds to elastin loss in chronic obstructive pulmonary disease. Interstitial lung diseases cause attenuation and distortion of the elastin scaffolding of alveoli such that discrimination between structures such as septal walls and microvessels becomes impossible. There is also reduction in fluorescence and distinctness of images. These changes correspond to biopsy specimens of usual interstitial pneumonia where elastin fiber destruction leads to irreversible alveolar damage. However, it is unclear if the changes on confocal scanning are due to only elastin damage or also caused by collapse of alveoli, inflammatory infiltration, and mucous impaction as well. Furthermore, the challenge with using any loss of features in diagnostic criteria is that it is difficult to be certain if the picture quality is due to the underlying pathology or poor probe deployment.

Case reports have already shown the potential for some interstitial lung diseases to be diagnosed based on specific positive findings. Pneumonitis secondary to amiodarone intake produces highly fluorescent macrophages even in nonsmokers. This is present with normal alveolar structure in the background without any overt elastin disorganization. In pulmonary alveolar proteinosis, unenhanced scanning shows alveoli filled with strongly fluorescent globular structures (100–300 μm) floating in mildly fluorescent fluid. These globules are lipoproteinaceous material as confirmed on bronchoalveolar lavage and are clearly distinct from alveolar macrophages. Alveolar integrity is again well preserved. The finding of thickened septal walls, granulomas, and dense disorganization may in future facilitate specific diagnoses such as asbestosis, sarcoidosis, and adenocarcinoma in situ, respectively.

Future Direction and Conclusion

Confocal microscopy is gaining increasing acceptance because a safety profile has been established across a range of patients with a variety of pathology. How much time it will add to flexible bronchoscopy especially if multiple lesions are being targeted or if navigation to focal lesions is complicated is unclear. It is also unclear if patients who are physiologically compromised will be able to tolerate these longer bronchoscopy sessions. To tackle this problem, confocal imaging has already been used successfully with other advanced bronchoscopic modalities such as autofluorescence imaging, radial endobronchial ultrasound, and electromagnetic navigation. These techniques help narrow down the field of scanning by either identifying abnormal bronchi or navigating to peripheral lung lesions. Confocal scanning can then be used to characterize these lesions, and a decision can be made on the need for biopsy.

Standardized descriptors and an expanded imaging atlas are still needed for both normal airways and pathology. Current structures that can be reliably identified are the basement membrane, microvessels, bubbles, fluorescent macrophages, and alveolar elastin framework. The distortion and disorganization of these structures need to be better characterized even as we search for other features. Correlation is needed not only with reference pathological samples but also with radiological descriptors on CT. Only then can the necessary randomized control trials be performed to study clinical utility. Meanwhile it remains to be seen if confocal microscopy can provide accurate, reproducible data that will clearly discriminate disease states. The immediate role may be to target biopsy sites and follow-up lesions rather than replace biopsy.

The pathognomonic features of standard histopathology, using, for example, hematoxylin and eosin stains, do not correspond directly to confocal images of alterations in elastin architecture. Research will be needed to better characterize pathological changes of elastin networks in conventional histopathology, while confocal microscopy needs to continue to improve because tremendous diagnostic information is lost by largely focusing on elastin. Using excitation light of differing wavelengths together with fluorescent dyes, collagen and flavins may soon be imaged as well. This will enable the epithelium above the basement membrane to be visualized. Molecular contrast with specific probes for precancerous lesions is also already being pioneered in gastrointestinal endoscopy. In addition, multiphoton microscopy and fluorescence-lifetime imaging hold much promise as adjuncts to confocal microscopy. Multiphoton microscopy utilizes infrared light, and each fluorophore is excited with two photons. This suppresses background signal, minimizes scattering, deepens penetration, and improves efficiency of light detection. Fluorescence-lifetime imaging is based on the differential decay rate of fluorescence and depends on the lifetime of the signal rather than the intensity.

Optical biopsy has opened up the possibility of noninvasive tissue sampling. This promises to be a quantum leap in diagnostic bronchoscopy. However, confocal microscopy remains but one of a number of competing technologies that are pioneering the field. Optical coherence tomography and endocytoscopy are two other techniques that already have data in ophthalmology and gastrointestinal endoscopy,

respectively. Optical coherence tomography is similar in principle to ultrasonography. A probe emits near-infrared light, and reflectance is detected to produce a cross-sectional image of the targeted tissue. The lateral resolution of 15 μm is limited compared to confocal scanning (3.5 μm), but the depth and field of view are both increased (2–3 mm). Endocytoscopy is essentially white-light microscopy via the bronchoscope using topical stains such as methylene blue. Both an integrated endocytoscope-bronchoscope and probe-based (3.2 mm) version that is placed through a larger, "mother" bronchoscope are being investigated. Color, en-face views that resemble conventional histopathology have been obtained with a lateral resolution of 4.2 μm and a depth of 50 μm. However, only surface scanning and generation of two-dimensional images is possible. Despite the relative limitations of each technology, the momentum in this field is accelerating toward improved targeting of bronchoscopic biopsy and eventually replacing it altogether.

Acknowledgment Dr. David S. Wilson, FCCP from the Lung Institute at Columbus Regional Hospital, Columbus, Indiana, USA, provided the confocal images in Figs. 22.3, 22.3, 22.4, 22.5, 22.7, 22.8, and 22.10.

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Optical Coherence Tomography

23

Ross G. Michel

Introduction

Optical coherence tomography (OCT) is a rapidly evolving imaging technology capable of generating real-time, high-resolution, cross-sectional images of complex living tissues. This technology is similar to ultrasound in that it measures phase and intensity differences of reflected or backscattered wave signals from tissues. However, unlike ultrasound which analyzes sound waves, OCT uses interference patterns from low-power, near-infrared light to generate topographical images. Compared to ultrasound, OCT systems have demonstrated greater sensitivity and much higher resolution of tissues in the lower respiratory tract. With a resolution of 10–20 μm at a penetration depth of 2 mm, images generated with OCT can provide the bronchoscopist with novel views of the lung at a microstructural level. This technology may in the future provide a noninvasive "optical biopsy" which could potentially guide the bronchoscopist to areas for biopsy or even obviate the need for conventional lung biopsies.

Principles of OCT Operation

Although an in-depth discussion of the concept of optical coherence tomography interferometry is beyond the scope of this chapter, a brief review of the principles of OCT operation may help the bronchoscopist to more effectively use this technology. As one may recall from prior study of physics, the speed of light greatly exceeds that of sound. Sound waves travel at a velocity of 1,500 m/s in comparison to light waves which move at a velocity of 3×10^8 m/s. Because light travels at such a high speed, a light time-delay system would require ultrafast time resolution which is currently impractical to achieve with modern electronics. For example, generating light-based images with a depth resolution of 10 μm would correspond to a time resolution of approximately 30 fs (30×10^{-15} s). In comparison, viewing tissues with a depth resolution of 100 μm with ultrasound requires an achievable time resolution of 100 ns (100×10^{-9} s). To solve the inherent difficulty of capturing rapidly moving light signals, currently available OCT time-domain systems measure light time delays by comparing backreflected light signals to a controlled reference signal.

Spatial information can be determined from the time delay of reflected light signals according to the formula $z = \Delta T \times v$, where z is the distance the light signal travels, T is the reflectance time delay, and v is the light wave propagation velocity (see Fig. 23.1).

To generate a two-dimensional high-resolution image using OCT, a near-infrared, high irradiance beam of light is emitted from a low-coherence light source. This beam of light initially passes into a beam splitter. One arm of the split beam is directed to a reference mirror and the other through the tip of a fiber-optic probe to shine upon a sample area (see Fig. 23.2).

The sample arm of the split beam is moved laterally along the surface of the tissue of interest. Currently available forward-facing probe devices use a miniaturized electromagnetic mechanism, coupled with an optical lens system to move the fiber-optic tip and provide lateral scanning of tissue over a 2 mm range. Signal intensity decreases as the light signal passes deeper into the tissues (see Fig. 23.3).

Light reflected from the tissues reenters the tip of the OCT probe. The backreflected light from the sample arm of the split beam recombines with the reference arm. The complete signal is delivered to a photodetector. Signal time-delay data in the photodetector is used to generate a real-time view of tissues on a microscopic level. These images can be displayed on an imaging console and saved electronically as digital images. As OCT technology is evolving, available

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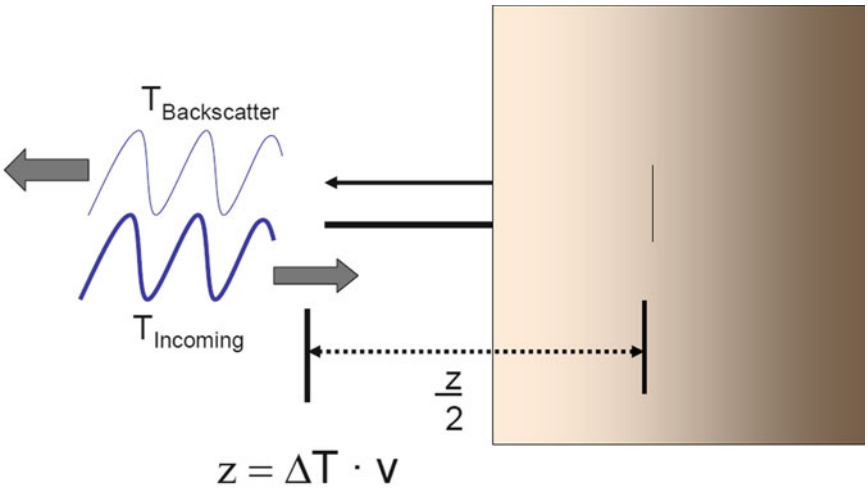

Fig. 23.1 Spatial information or distance (z) is determined from the time delay of reflected light (T) and the speed of light (v) according to the formula $z = \Delta T \times v$ (With permission from Chest, Michel et al.)

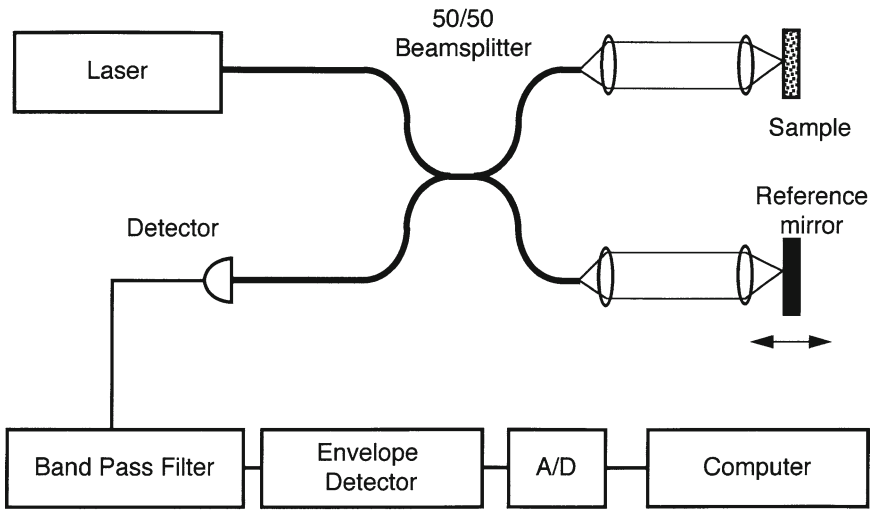

Fig. 23.2 Schematic of the fiber-optic implementation of an OCT System. OCT images are generated by performing successive measurements of optical backscattering versus depth at different transverse positions on the specimen (From Costas et al. with permission from the American Thoracic Society. Copyright © American Thoracic Society)

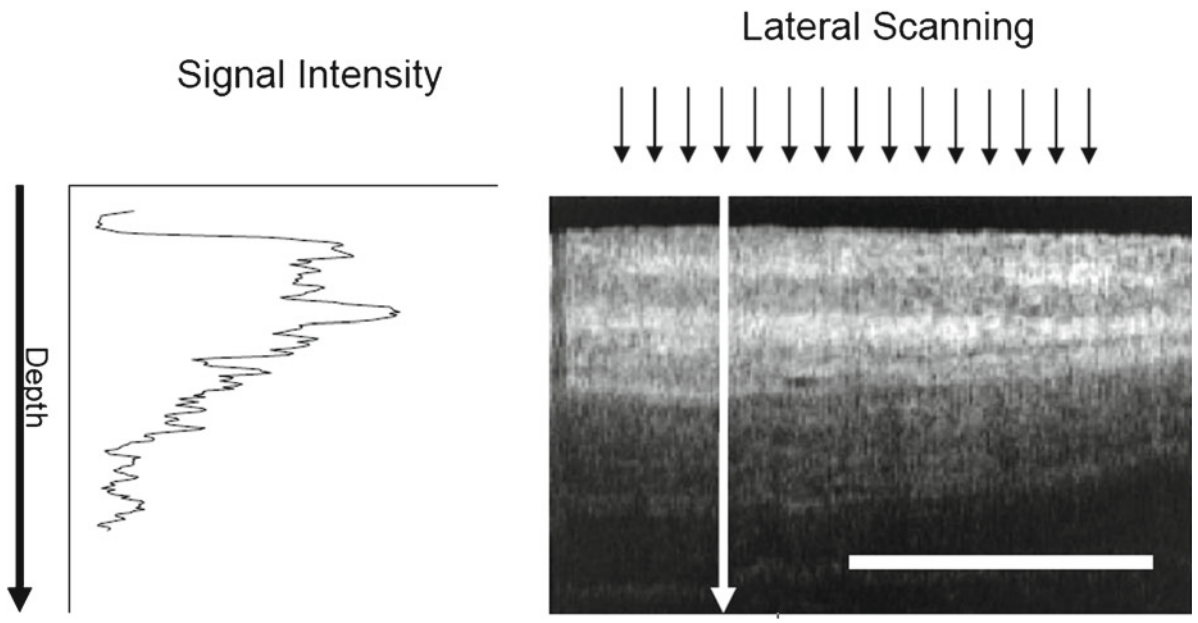

Fig. 23.3 OCT light signal intensity diminishes at increased tissue depth. Lateral scanning range is 2 mm. For reference, the white horizontal scale bar is 1 mm (With permission from Chest, Michel et al.)

equipment is improving. Current time-domain systems will likely be replaced by more advanced Fourier-domain systems. These newer frequency-based systems use spectrally separated photodetectors, allowing immediate depth scan calculations with enhanced imaging speed.

Early Use of OCT

The use of optical coherence tomography in clinical medicine was initially described in the early 1990s. The earliest and most extensive clinical use of OCT has been in the field of ophthalmology for retinal imaging in patients with macular degeneration. This technology has also been used by otolaryngologists and has been shown to be a feasible adjunct to awake transnasal laryngoscopy. OCT can clearly identify basement membrane violation and transition zones at cancer margins in patients with laryngeal cancer. Gastroenterologists have found that in vivo OCT correctly detected disease features of ulcerative colitis in endoscopically affected segments of colon with high sensitivity. This imaging technology has been studied for use by dermatologists for monitoring cutaneous inflammation and hyperkeratotic conditions. In cardiology, optical coherence tomography is being compared to intravascular ultrasound for characterization of coronary artery disease. OCT imaging has also been used by urologists and gynecologists to further characterize bladder and reproductive tract malignancies.

Optical coherence tomography has started to be used by pulmonologists to assist in the diagnosis and management of lung disease. Unlike ultrasound, light waves do not require a liquid-based coupling medium which may make OCT more compatible with airway imaging. OCT uses nonionizing, near-infrared light which has not been associated with any risks in the airways of humans. At this time, the use of this technology during bronchoscopy has been primarily for research purposes. OCT has proven to be capable of generating images of epithelium, mucosal layers, cartilage, and subepithelial structures in the animal and human trachea in multiple in vitro studies (see Fig. 23.4). OCT has also been shown to identify morphologic changes associated with inflammatory infiltrates, squamous metaplasia, and tumor presence in resected lung specimens (see Fig. 23.5).

Available OCT Equipment

Optical coherence tomography is a relatively new technology, and at this time, few OCT imaging systems are commercially available. Until recently, the only commercially available OCT system which was cleared by the Food and Drug Administration for use in the United States for lung imaging was the Niris Imaging System (Imalux Corp, Cleveland, Ohio). The Niris system includes an image console with a built-in light source that attaches directly to a long, reusable, flexible, fiber-optic, OCT probe. The distal tip of the OCT probe has an internal electromechanical lateral scanning mechanism encased in a rigid metal tip. In this system, the fiber-optic tip is moved back and forth along a linear axis to generate linear scans. In other OCT devices, the fiber-optic tip can be rotated to create radial scans. Radial scanning has been useful in coronary artery imaging and anatomic OCT which will be described in a later section.

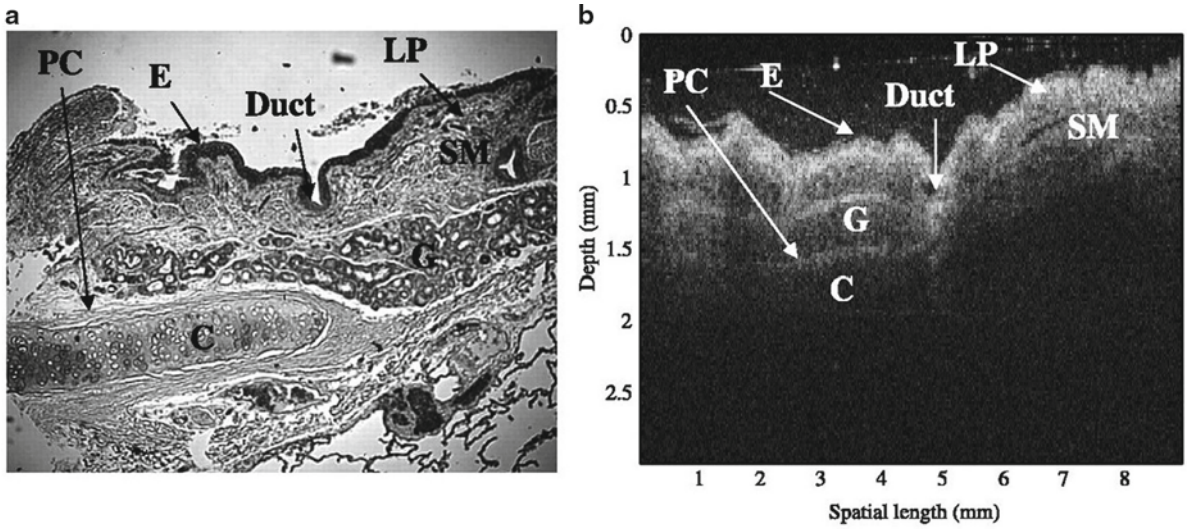

Fig. 23.4 Images of healthy human airways from resected lung specimens by standard histological section (**a**) (H&E stain; original magnification × 5) and OCT (**b**). *E* epithelia, *LP* lamina propria, *SM* smooth muscle, *PC* perichondrium, *C* cartilage (Awaiting permission from *Clinical Cancer Research*, Whiteman et al.)

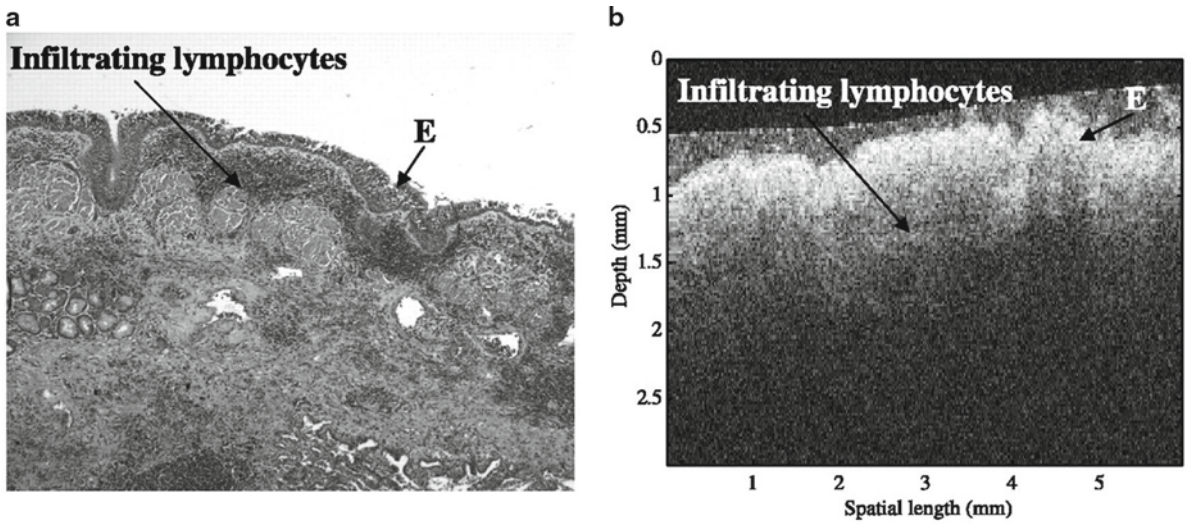

Fig. 23.5 Images of inflamed human airways from resected lung specimens by standard histological section (**a**) (H&E stain; original magnification × 5) and OCT (**b**). *E* epithelia (Awaiting permission from *Clinical Cancer Research*, Whiteman et al.)

Fig. 23.6 A currently available OCT imaging console (With permission from Imalux)

Although the outer diameter of the Niris flexible OCT probe is only 2.7 mm, the currently available model will not pass down the 3.2-mm diameter working channel of a standard therapeutic bronchoscope due to the length of rigid metal probe tip. This problem is currently being addressed by the manufacturer. The Niris OCT probe tip requires mucosal contact for lung tissue imaging. This probe can be sterilized after each use with conventional surgical sterilization devices. The lateral scanning range of this device is 2.0 mm with an image depth range of approximately 2.2 mm. The lateral resolution is approximately 25 μm with a spatial depth resolution of 10–20 μm. These imaging capabilities allow penetration through the upper layers of exposed tissues on airway surfaces where most airway neoplasms originate, and are equivalent to the tissue-sampling depth of conventional endobronchial forceps. The imaging console has a screen, keyboard, and multiple USB port outlets which can be used to save image data (see Fig. 23.6).

OCT During Rigid Bronchoscopy

The initial use of OCT for lower respiratory tract imaging in patients in the United States has been during rigid bronchoscopy. Once the rigid bronchoscope is inserted and an area of interest is identified, a flexible OCT probe can be readily advanced through the scope and placed upon the site of interest to generate a topographical image. OCT features of tracheopathica osteochondroplastica as seen in a patient undergoing rigid bronchoscopy have been described. A multimodality bronchoscopic imaging platform including OCT in conjunction with endobronchial ultrasound has been used during rigid bronchoscopy to characterize recurrent respiratory papillomatosis of the trachea. The OCT features of this lesion described by Colt et al. included a layer of heterogeneous light backscattering and a layer of high-degree scattering, corresponding to central, fibrovascular, papilloma core noted on histology (Fig. 23.7). Although OCT use during rigid bronchoscopy has been demonstrated as technically

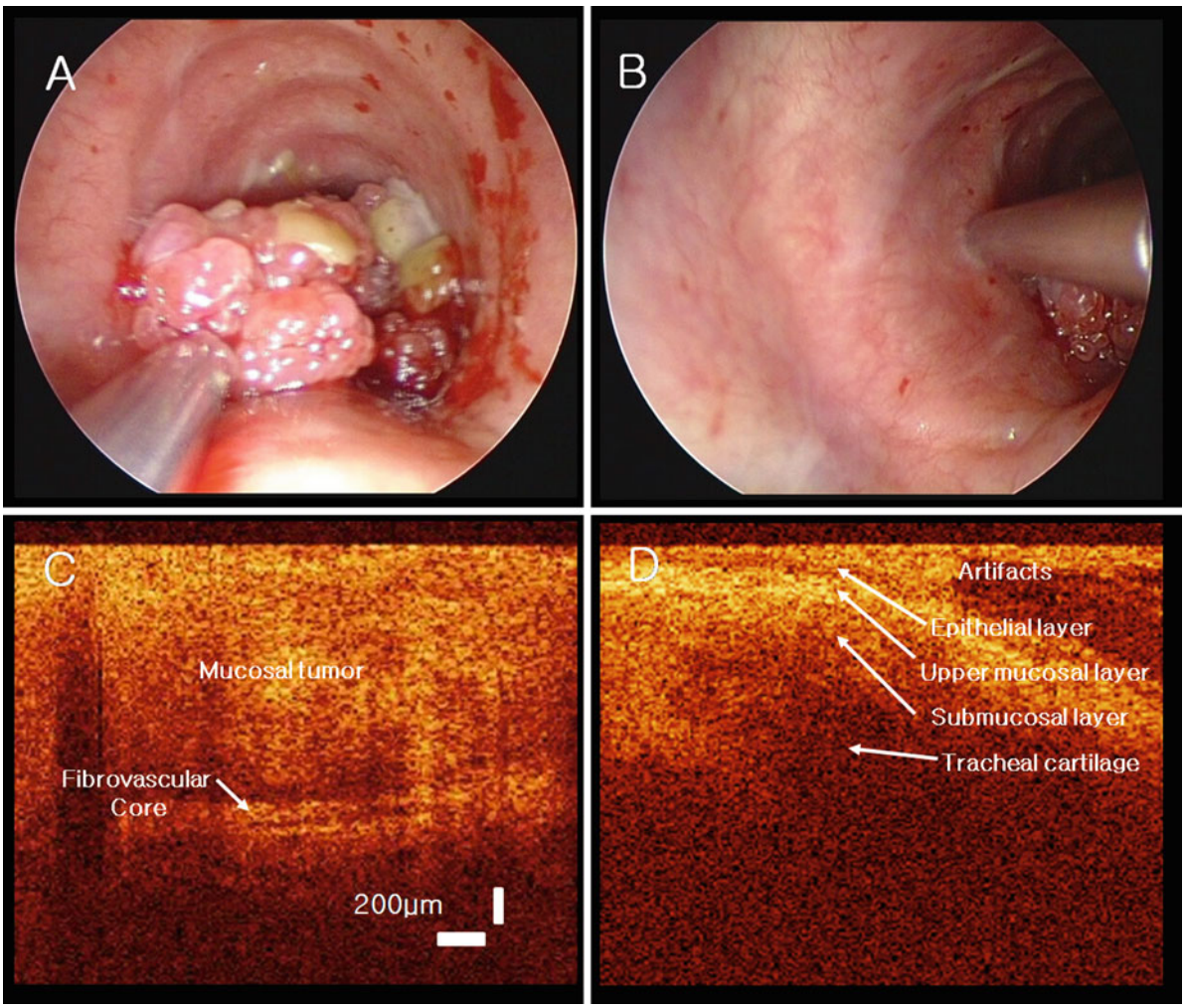

Fig. 23.7 OCT probe overlying an upper tracheal papilloma (**a**) and the normal tracheal wall (**b**). OCT images of the papilloma tumor and fibrovascular core (**c**) and the normal tracheal with mucosal structural layers (**d**) (With permission from Laryngoscope, Colt et al.)

feasible, in order to facilitate widespread routine use by pulmonologists, recent investigatory efforts have focused on the use of OCT during flexible bronchoscopy.

OCT During Flexible Bronchoscopy

The use of OCT with flexible bronchoscopy has been limited in the United States due to lack of commercially available FDA-cleared OCT devices that are compatible with standard flexible bronchoscopes. Multiple studies outside of the United States have investigated the use of optical coherence tomography with flexible bronchoscopy. In a study by Lam et al., a total of 281 radial scanning OCT images taken during flexible bronchoscopy were compared to corresponding biopsies. Autofluorescence bronchoscopy was used to identify airway sampling sites. A Lightlab/Pentax OCT probe was passed into the airways via the working channel of a flexible bronchoscope and used to generate radial OCT images. Quantitative measurements of the OCT images demonstrated that epithelial thickness of invasive carcinoma was significantly different from carcinoma in situ.

The first use of optical coherence tomography during flexible bronchoscopy in the United States was reported by Michel et al. in 2010. The results of this pilot study suggested that OCT is a technically feasible adjunct to flexible bronchoscopy in the diagnosis of lung cancer. Conventional OCT was performed using a commercially available Niris Imaging System, which is cleared by the Food and Drug Administration for use as an imaging tool in the evaluation of human tissue microstructure. An investigational device exemption for the use of this OCT system during flexible bronchoscopy for lung imaging was approved by the FDA for this study.

In the study by Michel et al., an OCT probe was introduced into the airways of patients with an endobronchial mass during flexible bronchoscopy. The OCT probe tip was attached to the exterior of the flexible bronchoscope (see Fig. 23.8) and placed upon desired sample sites under direct visualization. Linear

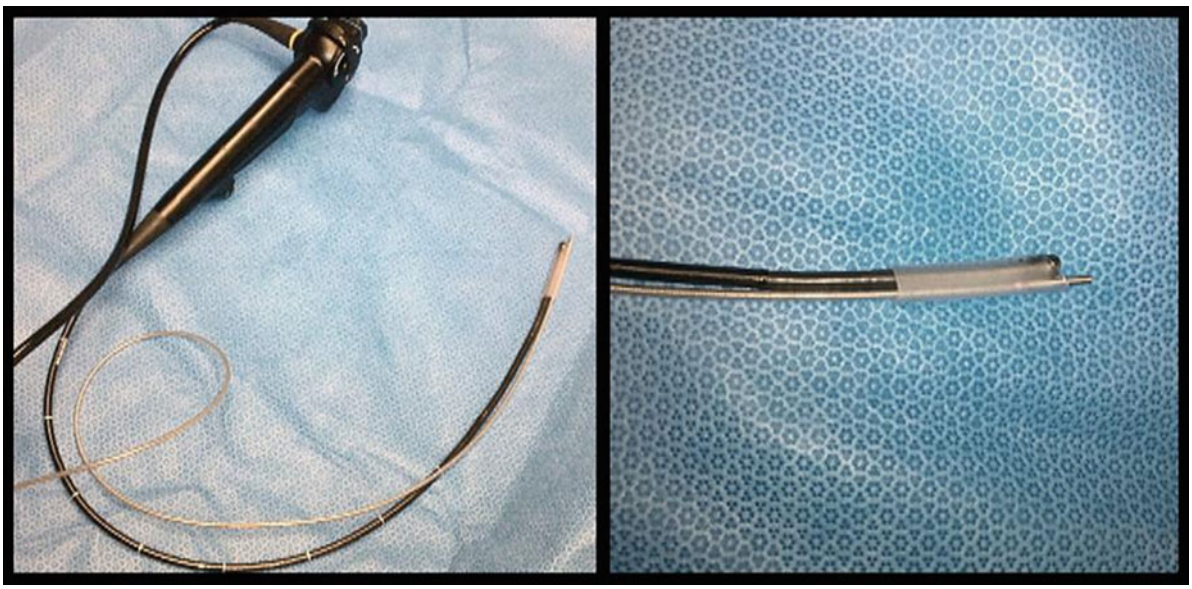

Fig. 23.8 Flexible bronchoscope with the OCT imaging probe attached to the scope exterior using a size 28 French polyvinyl-chloride nasal airway (With permission from Chest, Michel et al.)

OCT scans of an endobronchial mass and a control area of normal bronchial mucosa were obtained in five patients. The imaged sites were biopsied for pathologic correlation. A library of 60 OCT images with corresponding endobronchial biopsies was generated. The average procedure time was 29 min. Although OCT during flexible bronchoscopy appears to be feasible, it remains technically difficult with the currently available FDA-approved devices. Using the Niris OCT probe on the exterior of the flexible bronchoscope resulted in limited scope flexion, causing somewhat difficult passage of the scope through the upper and lower airways. FDA approval of an OCT probe that passes down the working channel of a standard flexible bronchoscope is needed for practical application of this technology in the United States. "Double-barrel" external endoscopic sheaths through which OCT probes can be introduced as well as newer OCT probes which are accommodated by the working channel of standard flexible bronchoscopes are currently being developed.

Interpretation of OCT Images

Interpretation of OCT images in the lung is an evolving field of study which is currently being forwarded by both pathologists and pulmonologists. OCT allows the bronchoscopist to identify microstructural features of the lung in real time. The sensitivity and specificity with which lung inflammatory and neoplastic changes can be visualized by OCT in patients is currently under investigation. To date, most studies have involved comparison of OCT images to histopathology from lung biopsy specimens. In the previously mentioned study by Lam et al., bronchial epithelial thickness of invasive lung carcinoma as identified by OCT was significantly greater than that of carcinoma in situ. Quantitative measurements using OCT also showed that epithelial thickness of bronchial dysplasia was significantly greater than that of metaplasia or hyperplasia. Additional OCT features of malignancy included basement membrane changes and more discernable nuclei (see Fig. 23.9).

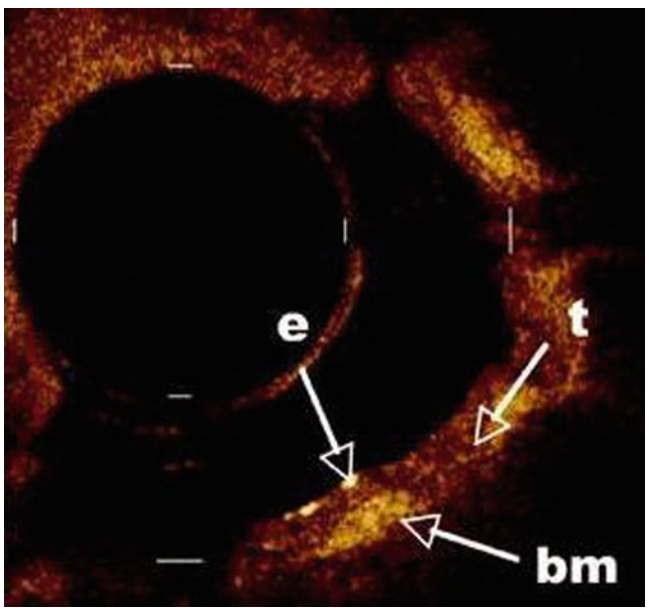

Fig. 23.9 Radial OCT image of invasive lung cancer. Note the disruption of the normal epithelial (*e*) and basement membrane (*bm*) layers infiltrating tumor (*t*) which has more discernable nuclei (Awaiting permission from Clinical Cancer Research, Lam et al.)

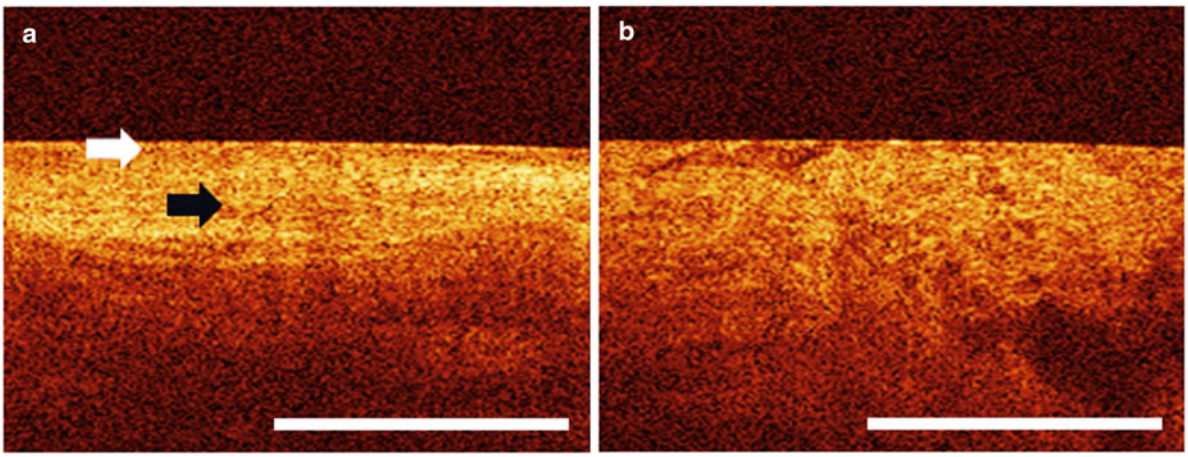

Fig. 23.10 OCT images in patient with small-cell carcinoma. An image from normal bronchial mucosa (**a**) shows normal layers of epithelium (*white arrow*) and lamina propria (*black arrow*). An image from the tumor area (**b**) shows loss of identifiable microstructures. The *white* reference bar is approximately 1 mm (With permission from Chest, Michel et al.)

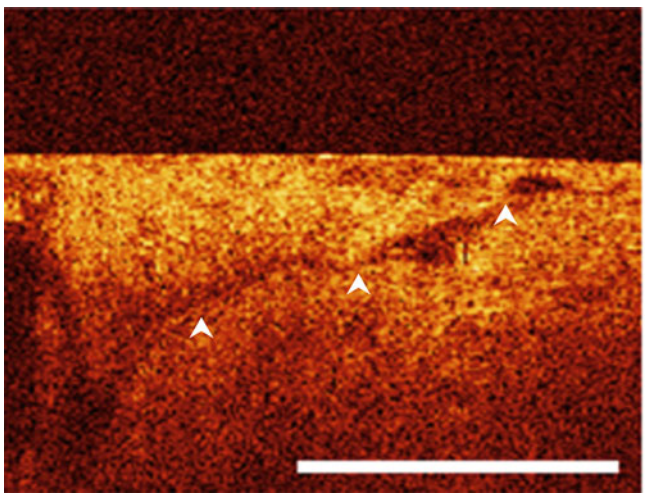

Fig. 23.11 "Optical fracture" in an OCT image from a patient with small-cell carcinoma of the lung. This ragged, irregular, dark line between two light areas in the subepithelium (*white arrows*) has been seen in OCT images of neoplastic lesions (With permission from Chest, Michel et al.)

In the study by Michel et al., OCT images of malignant and benign endobronchial masses were compared to those from areas of normal bronchial mucosa. The microstructural characteristics of normal bronchial mucosa including epithelium and lamina propria were able to be identified using OCT. A consistent OCT feature of malignancy was the loss of these normal, identifiable microstructures. Smooth, linear patterns of normal epithelium and lamina propria were lost on OCT images of infiltrative neoplasms (see Fig. 23.10). Another OCT feature of lung neoplasia was subepithelial "optical fracture" of tissues. OCT images from neoplastic lesions displayed irregular, ragged, dark lines between two light areas that had the appearance of a fracture in the subepithelium (see Fig. 23.11). The mechanism of optical fracture is uncertain. As infiltrative carcinomatous tissue tends to be more fibrotic than the surrounding normal tissue, it is believed that optical fracture is due to the interference pattern of backscattered light from an interface of two distinct tissue densities which are found in tumors. Further studies are under way at multiple medical centers to help bronchologists consistently identify OCT patterns of pathologic lung lesions.

Anatomic Optical Coherence Tomography

Anatomic optical coherence tomography (*a*OCT) is an adaptation of conventional OCT that can be used to generate macroscopic cross-sectional views of the airways during flexible bronchoscopy. While conventional OCT provides microscopic subsurface images of the airways, *a*OCT enables the bronchoscopist to perform quantitative scans of airways up to 7.2 cm in diameter. Increasing the axial scanning distance from 3 mm at the OCT probe tip to approximately 3.6 cm has been proven successful in providing accurate measurements of the diameter and cross-sectional areas of the airways. Cross-sectional images of airways similar to those of axial CT scan can be made by the bronchoscopist in real time (see Fig. 23.12). Williamson et al. demonstrated that *a*OCT can be used to guide selection of stents for tracheal stenosis and characterize the severity of tracheomalacia. Anatomic OCT has the potential to reduce the need for patient exposure to the ionizing radiation of CT scans to characterize large airway narrowing tumors and to improve outcomes in patients with stentable lesions.

Williamson et al. also demonstrated that a pullback, rotational *a*OCT scan was able to identify a patent distal left main bronchus beyond a large proximal left main bronchus tumor.

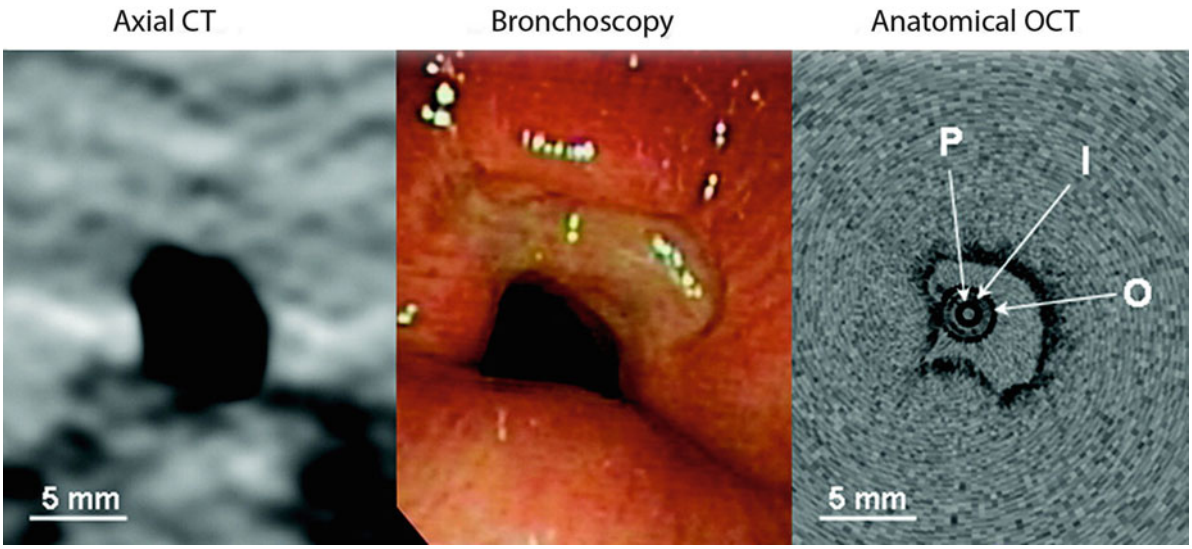

Fig. 23.12 An area of subglottic stenosis as seen by CT scan, bronchoscopy, and an anatomic OCT. The central circle (*P*) indicates the aOCT probe itself. The inner wall (*I*) and outer wall (*O*) of the surrounding plastic catheter are shown (Awaiting permission from Chest, Williamson et al.)

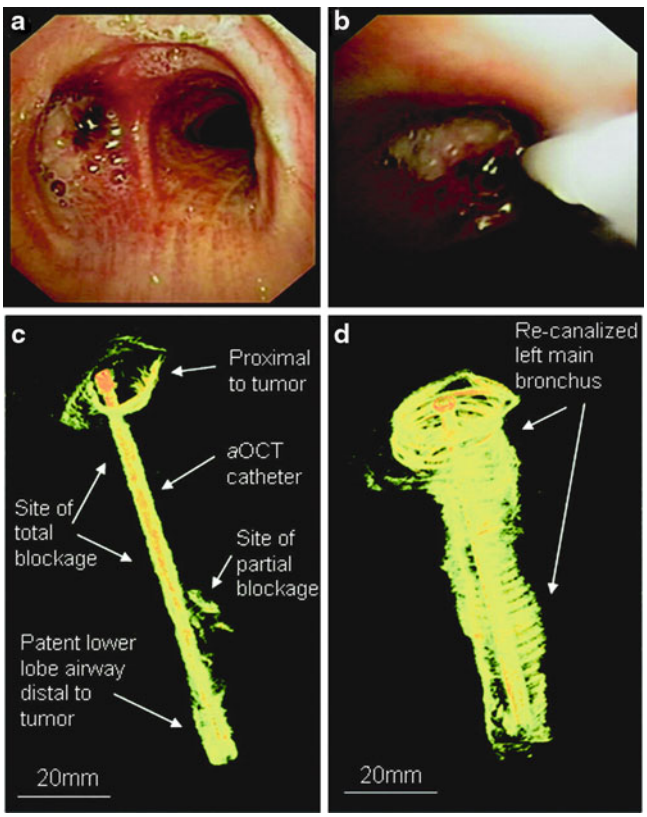

Fig. 23.13 Bronchoscopic view of a tumor in the left main bronchus. (**a**) An aOCT probe is advanced beyond the tumor (**b**). 3D reconstruction of an aOCT scan showing patent left lower lobe airway beyond the tumor (**c**). 3D reconstruction of an *a*OCT scan showing the now patent left main bronchus after endobronchial resection and chemotherapy (**d**) (Awaiting permission from Chest, Williamson et al.)

In his report, the airway beyond the obstructing malignancy was unable to be viewed bronchoscopically due to inability to pass the scope beyond the lesion. The narrower OCT probe was able to pass the lesion and demonstrate a partially patent, large, distal airway. This patient underwent endobronchial resection using an Nd:YAG laser and subsequent radiation therapy and chemotherapy. 3D reconstructions from the *a*OCT images demonstrated restoration of patency of left main bronchus (see Fig. 23.13).

Conclusion

Optical coherence tomography is a powerful technology that shows great promise in diagnostic pulmonary medicine. There are ongoing clinical trials at multiple medical centers that will help to better define the role of OCT in the early recognition of lung cancer and also in the evaluation and monitoring of microstructures in the lower respiratory tract that are affected by other invasive or inflammatory disease processes. OCT could potentially be used in conjunction with endobronchial ultrasound, autofluorescence bronchoscopy, or narrowband imaging to guide the location of biopsies. If the preliminary studies are confirmed, OCT technology may provide a noninvasive "optical biopsy," which could potentially obviate the need for conventional biopsies, particularly in patients with high risks for biopsy-related complications, such as bleeding. Anatomic OCT has been demonstrated to be a useful tool to provide real-time quantitative measurements of airway dimensions (see Table 23.1).

Table 23.1 Possible indications for optical coherence tomography during bronchoscopy

◦ To assist in the identification of neoplastic, preneoplastic, infiltrative, or inflammatory lung diseases such as lung cancer, sarcoidosis, or asthma
◦ To guide the location and increase the diagnostic yield of endobronchial or transbronchial lung biopsies
◦ To provide real-time measurements to characterize the severity of airway stenosis, tracheomalacia, or bronchomalacia and assist with selection and placement of airway stents (anatomic OCT)
◦ To provide a diagnostic "optical biopsy" and potentially obviate the need for conventional biopsies in patients at high risk for biopsy-related complications

Limitations to the routine use of optical coherence tomography during bronchoscopy have included factors related to both available equipment and interpretation of OCT images. Initial use of OCT during flexible bronchoscopy in the United States required the attachment of OCT probes to the exterior of the bronchoscope, resulting in limited scope flexion and somewhat difficult passage of the bronchoscope through the upper and lower airways. Commercially available OCT systems offering flexible probes that can be accommodated by the working channel of a flexible bronchoscope are gaining FDA approval and are becoming more widely available. The cost of a currently available FDA-approved OCT imaging system including an imaging console, software, and a single reusable flexible, fiber-optic probe is approximately $50,000. As with other bronchoscopic imaging techniques, the bronchoscopist should expect to encounter a learning curve for both the acquisition and interpretation of OCT images.

At this time, further studies are needed to determine the sensitivity and specificity with which OCT technology can be used to identify disease in the lower respiratory system. Although optical coherence tomography is not currently practical for widespread use with bronchoscopy, ongoing research and technologic improvements will likely lead to more use of OCT by pulmonologists. In the future, use of OCT in combination with other imaging modalities may provide increased diagnostic yield and therapeutic benefit from bronchoscopy.

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Image-Guided Bronchoscopy

24

Rabih Bechara

Introduction

In recent years, the role of pulmonary medicine has evolved from simply diagnostic to offering potential therapeutic interventions to patients with pulmonary lesions. The accuracy in the approach to these lesions directly affects the success or failure of the procedure. For the diagnosis of pulmonary lesions, bronchoscopy is routinely considered because it is safe and minimally invasive. However, its overall diagnostic yield is inadequate with a diagnostic yield of 57% for all lesions and 34% for lesions less than 2 cm in diameter. The factors affecting the transbronchial diagnosis of pulmonary lesions include the lesion size, its location, the presence/absence of bronchial involvement, and its malignant/benign status. The bronchoscopist-associated factors include the technology used and the bronchoscopist's skills and experience. At present, bronchoscopy for pulmonary lesions is performed using a bronchoscope with an external diameter of approximately 5–6 mm or ultrathin scope with an external diameter of 2.8 mm or less. Navigation is usually under x-ray fluoroscopy. The bronchoscopists mentally reconstruct the three-dimensional (3D) bronchial arrangement based on two-dimensional (2D) planar axial slices of CT, performed before the procedure, and select a bronchial path. A major problem with this method is difficulty in selective guidance for the bronchoscope and its accessories, peripheral bronchial path selection, and at the same time maintaining the position of the bronchoscope along with its accessories in desired location. New technology allows direct guidance and navigation and has shown to be safe and accurate. The use of these methods increases yield and carries a low risk of complications to the patient.

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Virtual Bronchoscopy

VB is a method for a 3D fly-through display viewed from the bronchial lumen, as if it were observed using a bronchoscope. Multiplanar reconstruction can display any cross-sectional image (planar axial, sagittal, and coronal sections) useful in gaining an understanding of the lung structure including the airway. Unfortunately, direct use of this data for the guidance of the bronchoscope is difficult. VB is non-invasive and has no adverse effects except radiation exposure. VB allows the display of areas peripheral to the stenotic lesion and also the display of extramural structures simultaneously with endobronchial images using the volume rendering method. Therefore, VB has been used for the evaluation of airway stenosis, tracheal/bronchial injury, endobronchial malignancy, and postoperative bronchial complications (Fig. 24.1). As such, it plays an important role in the patient's evaluation in the planning of stent placement, surgical airway resection, dilation of stenotic lesions, and therapeutic interventions such as photodynamic therapy, brachytherapy, and laser ablation. Used by itself, VB plays little role in procedure guidance.

Virtual Bronchoscopy Navigation and Systems

Virtual bronchoscopy navigation is a VB method clinically applicable to arrive at the peripheral lesions. Virtual images of the bronchial path to the lesion are produced and used for navigation and guidance during real-time bronchoscopy. Unlike the virtual bronchoscope, the tip of the real bronchoscope can only be moved up or down so that appropriate rotation is always necessary for adequate navigation and airway visualization. But when the bronchoscope is rotated, the real image shifts from the virtual image. Therefore, synchronization of the virtual and real images is necessary especially at each branching; otherwise, the risk of disorientation becomes significant. To overcome these issues, systems for

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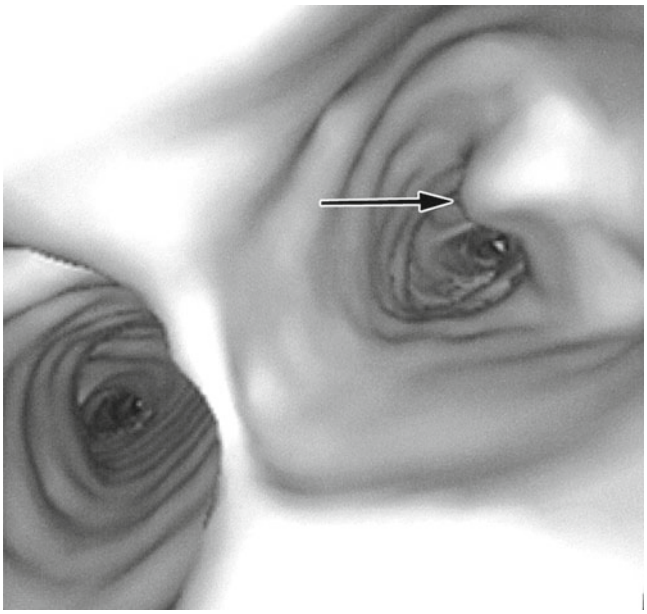

Fig. 24.1 Virtual bronchoscopy showing and endobronchial lesion (*arrow*)

clinical use have been developed recently, and data collection is in progress.

Systems in this category include, but are not limited to, the VBN system (*Bf-NAVI*; KGT, Olympus Medical Systems, Tokyo, Japan) and the LungPoint System by Broncus Technologies. The former system is characterized by the automatic production of VB images along the bronchial path and the display of VB synchronized with real images for bronchoscopic navigation. Bronchoscopists initially input the digital imaging and communication in medicine (DICOM) data of CT images into the system. A CT slice thickness of less than or equal to 1 mm is desirable. Then, the starting point in the trachea is chosen. An appropriate threshold is automatically adjusted, and bronchi to peripheral areas are extracted. Finally, the target is set as well as the terminal point. While observing short-axis, sagittal, and coronal images, the operator selects the lesion and the bronchus closest to it as the target and terminal point, respectively (Fig. 24.2).

Because the extracted bronchi are indicated in blue, the bronchi involved with the lesion are clearly observed all the way up to the proximal area on the monitor confirming that each branching is extracted. Importantly, alternative manual path extraction can be added. When the target and terminal point are determined, the path to the terminal point is automatically searched and displayed. When the point in the path is moved from the starting to the terminal point, each corresponding cross-sectional image is displayed and the branching and extraction status in the path are reconfirmed. The path is also displayed in the bronchial tree. When the path is determined, VB images along the path are automatically produced. While VB images are moved from the starting to terminal point, the bronchus for the insertion of the bronchoscope at each bronchial branching is marked and registered as a thumbnail (Fig. 24.3).

The time required from the insertion of DICOM data of CT into the system to the completion of thumbnail registration is approximately 15 min, of which half used for manual setting and confirmation. The median range of the production of VB images using this system is the sixth-generation bronchi. VBN is performed while displayed VB images of the target bronchus are synchronized with real-time endoscopic images by image rotation, advancement, and retreat. Concretely, the VB image that diverges from the real image because of the rotation at the time of bronchoscope insertion is made consistent with the real image using the rotation function. Subsequently, the VB image is advanced to the next bronchial branching, and the bronchoscope is similarly advanced. This procedure is repeated. Because the bronchus to which the bronchoscope is advanced is displayed on the VB image at each branching, the bronchoscope is advanced to the target based on this display. When branching is lost during bronchoscopic advancement, VB images are redisplayed, and a thumbnail at each branching is provided as a reference. The direction of the lesion is displayed on the image and can also be referred to.

Most of the data about the safety, efficacy, and yield of this system comes from the Far East. Together, there are eight studies with a total of 428 lesions (317 lesions less than 2 cm); the diagnostic yield was 73% (67% for lesions less than 2 cm).

The LungPoint Virtual Bronchoscopic Navigation System (Broncus Technologies, Inc., Mountain View, CA) is computer-assisted image-based navigation software that enables the bronchoscopist to navigate and localize a targeted area of interest in the lung. The system requires thin-section CT scans in the order of 1.25-mm slice thickness with an interval spacing of 0.0625 mm or less. Scans at total lung capacity (inspiratory breath-hold) are preferred so that the smaller airways are expanded. The system has the capacity to import scans in standard Digital Imaging and Communications in Medicine format either from a compact disk or across the network. Once imported, the images are automatically analyzed by the LungPoint software. This involves segmenting airways 3 mm and greater in diameter and major vessels by calculating a centerline (central axis) for each airway. Along with airway segmentation, endoluminal renderings of the airway structure are modeled to produce a virtual bronchoscopic view. Once the target object is placed, the software calculates up to three pathways through the airways to reach it. These pathways are calculated to reach the points closest to the target. Three-dimensional images of the airway tree and target as well as the virtual bronchoscopic animation enable assessment of the calculated pathways. The CT projections are also available and update as the animation progresses

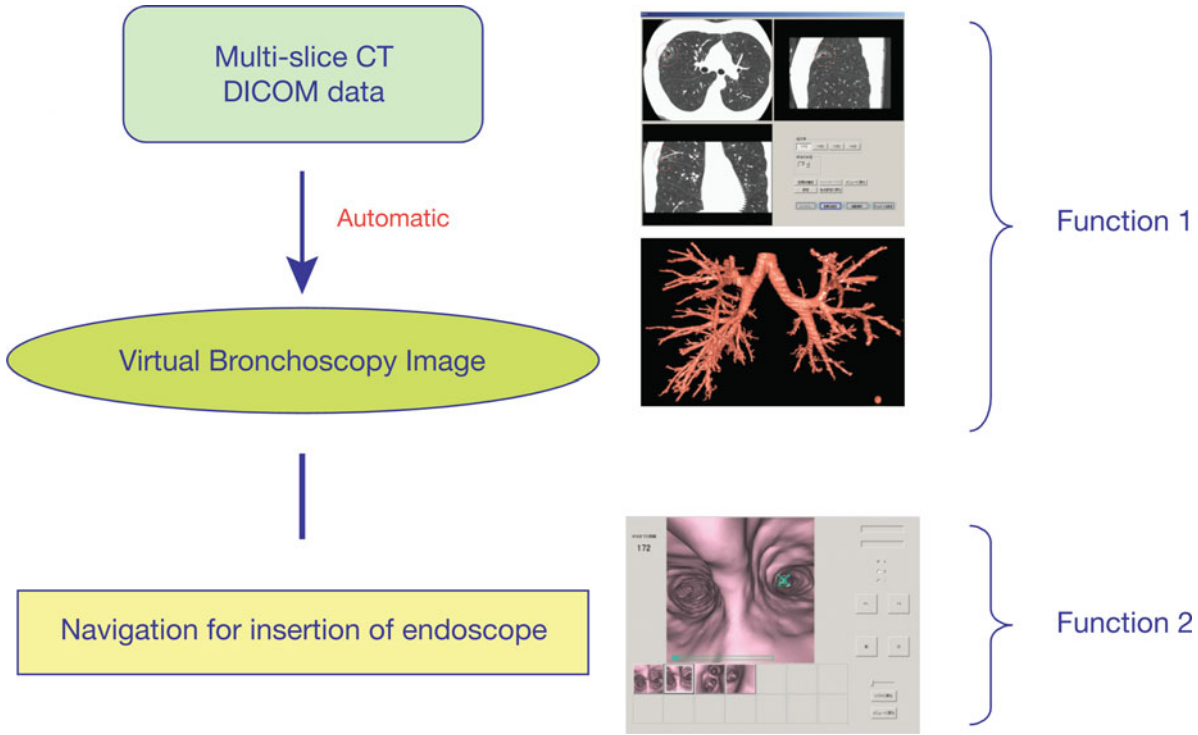

Fig. 24.2 Steps in the setting of the BF-NAVI system

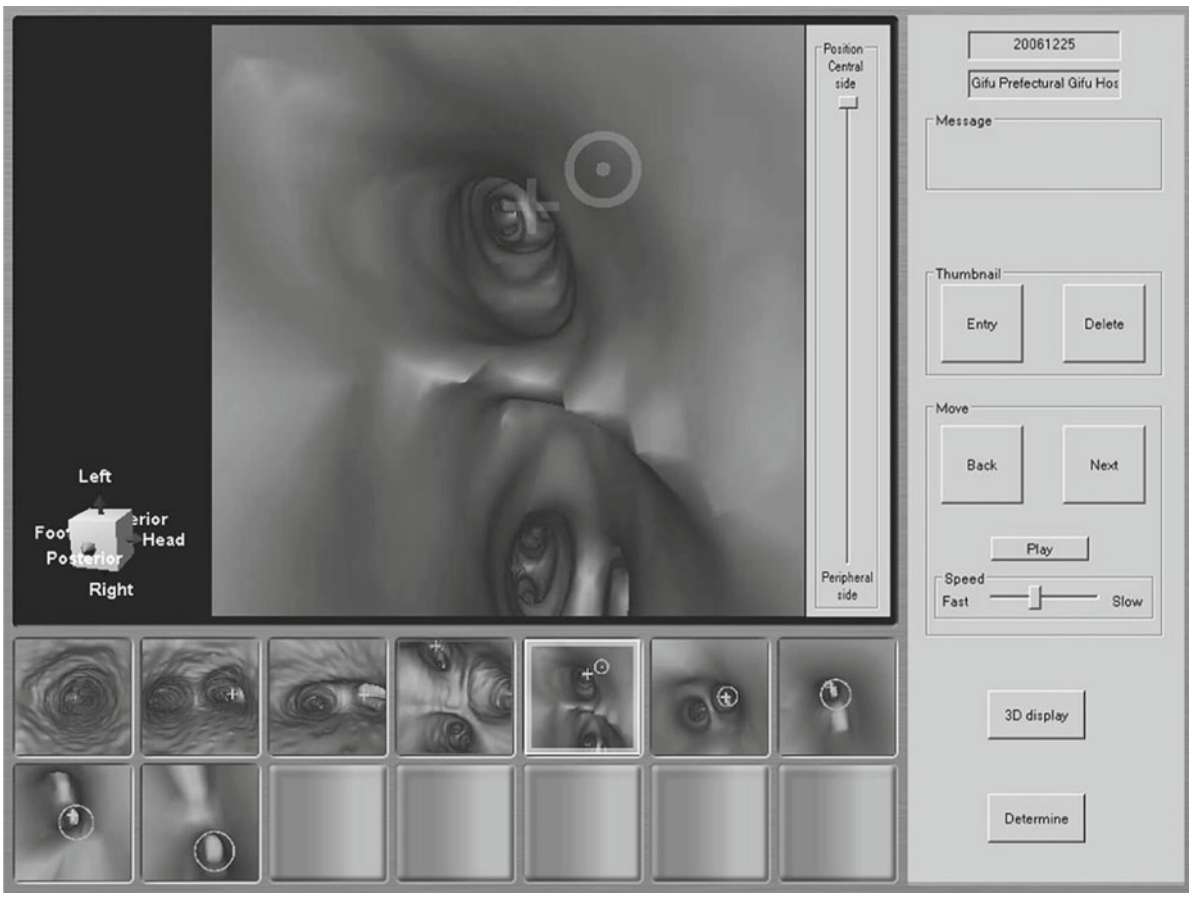

Fig. 24.3 Display of the VB-NAVI system

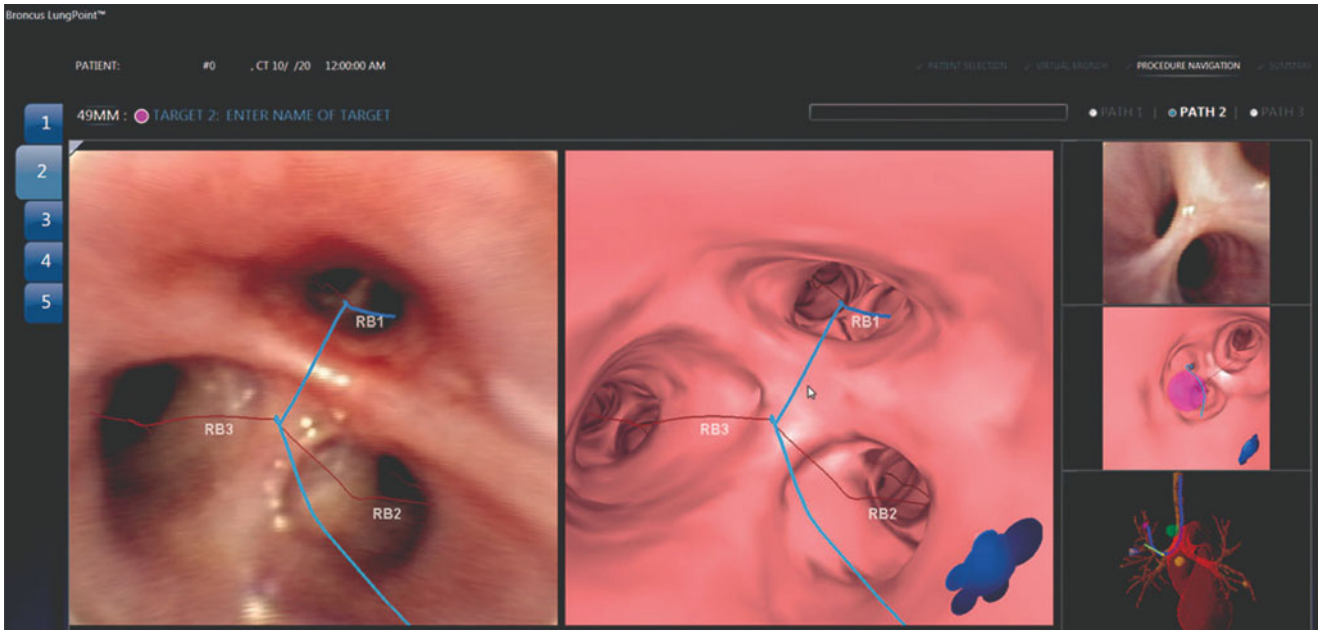

Fig. 24.4 Pathway projected on the virtual (*right*) and real image (*left*) on the LungPoint system

through the airway toward the target. The navigation system displays two main images: the live bronchoscopic video and the VB animation (Fig. 24.4).

The animation represents the pathway that was selected during the planning process. An image-based synchronization technique aligns the virtual images with the anatomy seen in the live bronchoscopic video. An assistant can facilitate this process by advancing and adjusting the virtual bronchoscopic rendering. When the two images are synchronized, the software calculates the position of the bronchoscope in the airway and overlays the pathway to the target on the actual bronchoscopic video image. Adjacent major vessels as well as the target are overlaid on the airway wall. Data on the safety and diagnostic yield of this system is being collected. One series from Germany included 25 subjects (9 women and 16 men, mean age 67 years) with 25 lesions (mean size 28 mm). Using this navigation system, the bronchoscope could be advanced along the planned route in all cases. In 14 of the cases (56%), the bronchoscope could be advanced all the way to the lesion bronchus. The planning time was a median of 5 min, and the median examination time was 15 min. A definitive diagnosis was possible in 20 cases (80%). One patient experienced a small pneumothorax because of the biopsy that resolved without drainage. No other complications occurred.

It is important to remember that VBN-supported bronchoscopy is not providing real-time guidance, as the instrument is not registering as it moves along. Additionally, instrumentation cannot be guided with this approach.

Electromagnetic Navigation

EMN-guided bronchoscopy solves some of the problems of VBN-based guidance. The instrument position is registered in real time within an electromagnetic field, and instruments can equally be tracked. EMN-based navigation has been in clinical use in neurosurgery and vascular medicine, and several such systems are commercially available now for respiratory applications. Examples include the Superdimension and the Veran guidance systems.

When using the Superdimension process, the heart of the electromagnetic system is the locator guide and the magnetic locator board (Fig. 24.5). Performing the navigation procedure is a three-step process. The initial stage (the planning phase) is done prior to the procedure. The patient must have a high-quality CT scan of the chest (there is no need for contrast material) with cuts of 1.5 mm or less and a 1.0-mm overlap. The later criteria provide adequate resolution for the system to create a 3D map of the airways. It also provides cuts of the lung in coronal, sagittal, and longitudinal planes. The physician then marks the affected area to which navigation is desired (Fig. 24.6).

The system reconstructs a 3D-airway map and suggests a pathway to the chosen target. Note that the navigator can add, delete, or modify pathways as deemed necessary. Multiple targets can be marked at once, and multiple navigations can be performed. In the second or registration phase, the patient is brought into the procedure suite which has previously been mapped to account for all interfering magnetic fields. There, he is then placed on a stretcher on

Fig. 24.5 Steerable guide (*left*) and magnetic locator board (*right*)

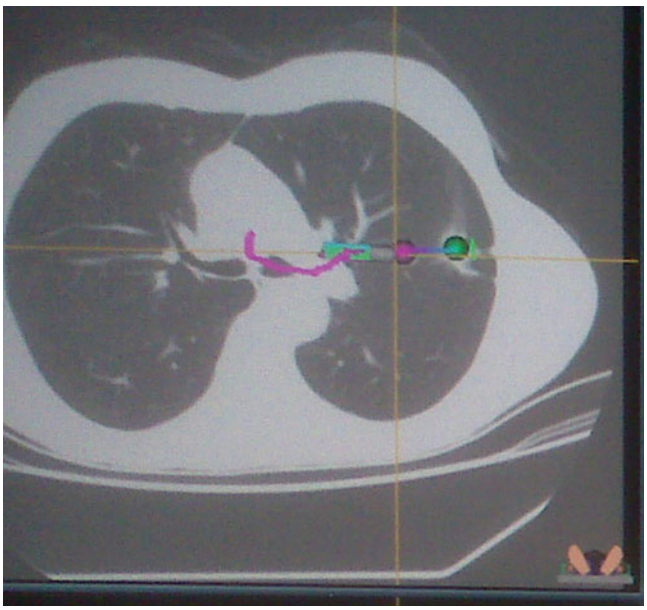

Fig. 24.6 Target chosen and marked in *green*

the locator board. Three sensors are placed on the body as markers. As the bronchoscopy is performed, locator probe is passed through the bronchial tree sending back information so that the system is able to match it to the information contained in the CT scan used in the planning phase. As such, the software constructs suggested pathways to the targets chosen. In the final navigation phase, the suggested pathway is displayed on the virtual view (Fig. 24.7). The latter is manually synchronized to the real bronchoscopic display to prevent disorientation.

Once navigation is beyond natural vision through the scope, a steerable catheter is used to navigate to the lesion. The system displays a multiscreen demonstrating the local and tip views seen by the steerable guide. The navigation is performed using the specially designed locator guide; it is able to rotate 360° using the small dial at the neck of the catheter. Then by pulling the neck back, it is flexed in the direction the arrow on the catheter is pointing. The setting of the directional steerable guide inside the catheter is shown in the lower right portion of the navigation screen by arrows seen in the orange circle. Progress is followed by the relative locations of the green dot inside the yellow circle. The larger and more centered the dot, the closer the locatable guide is to the lesion. As such, the locator guide is steered through the tracheobronchial tree until the target is reached (Fig. 24.8).

Since the publication of initial animal studies in 2003, a substantial body of literature demonstrating the safety of the system has been established. The efficacy of the system is harder to determine, as most publications report on retrospectively reviewed uncontrolled case series and are methodologically insufficiently well designed. In two studies looking at diagnostic yield, Schwarz et al. found result to be 69%, and there were no reported serious complications. Gildea et al. reported an overall diagnostic yield of 74% with peripheral lesions of which 57% were less than 2 cm. In that retrospective study, the authors yield was 66% and 100% for lesions 2–4 cm and >4 cm, respectively. Importantly, in their correlation analysis, no significant relationship between diagnosis and size or location of peripheral lesions was found ($p > 0.05$). Similarly, Eberhardt reported yield independent of lesion size, but in his manuscript, location of the lesion tended to affect negatively the outcome in the lower lobes (yield 29% compared to 59%). In addition, when the system is able to match the patient to the CT scan with a discrepancy of <4.4 mm, the diagnostic yield has been reported to be 71% compared to 40% when the match is >4.4 mm. One potential explanation is that the

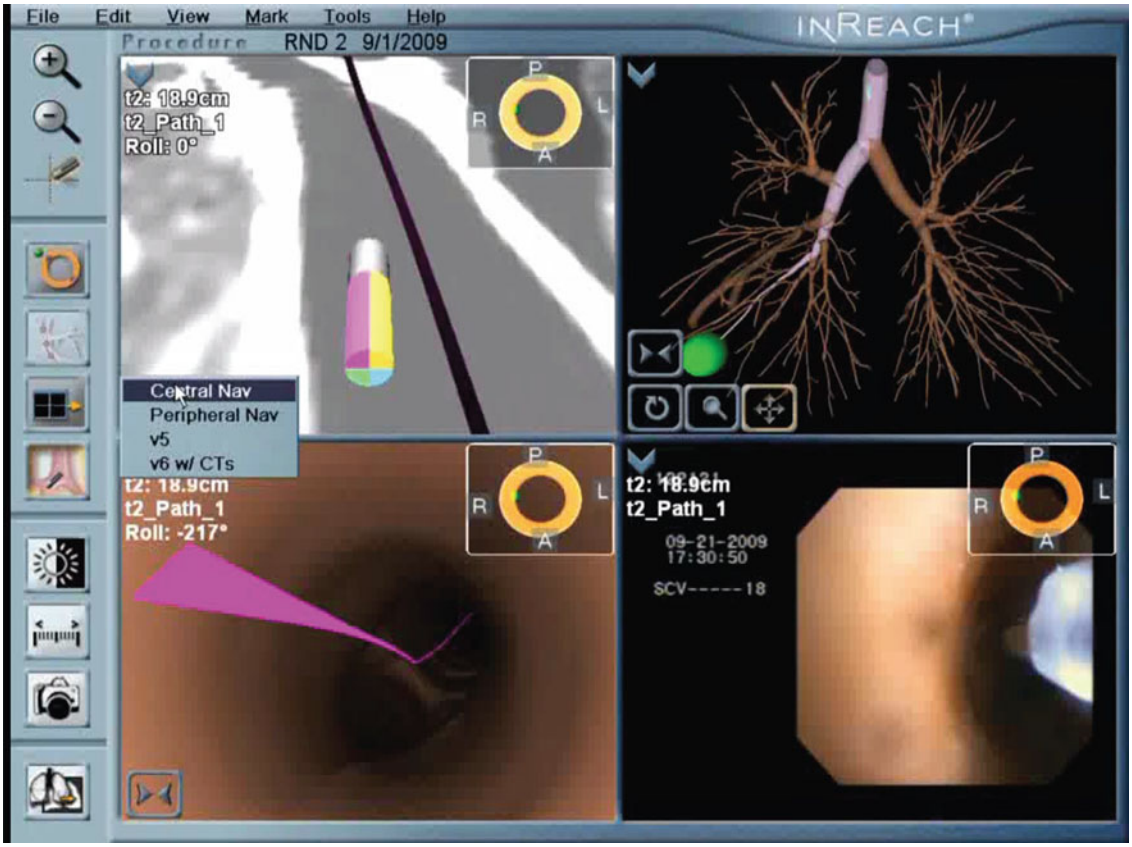

Fig. 24.7 Suggested pathway displayed on the virtual image (*left bottom*). Steerable guide in airway on real image (*bottom right*). Tracheobronchial tree showing target and pathway (*top right*). Tip of the locator guide in airway (*top left*)

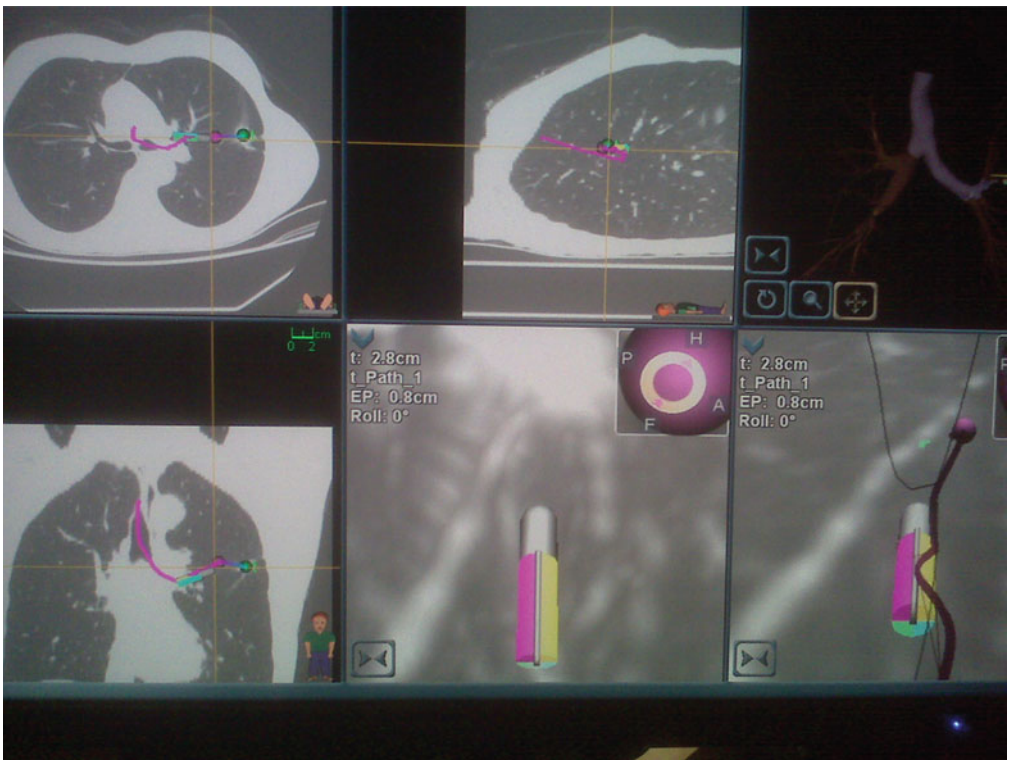

Fig. 24.8 Sagittal, coronal, and transverse CT cuts showing locator guide and target. Local view and tip view of the locator guide (*bottom mid* and *right*, respectively)

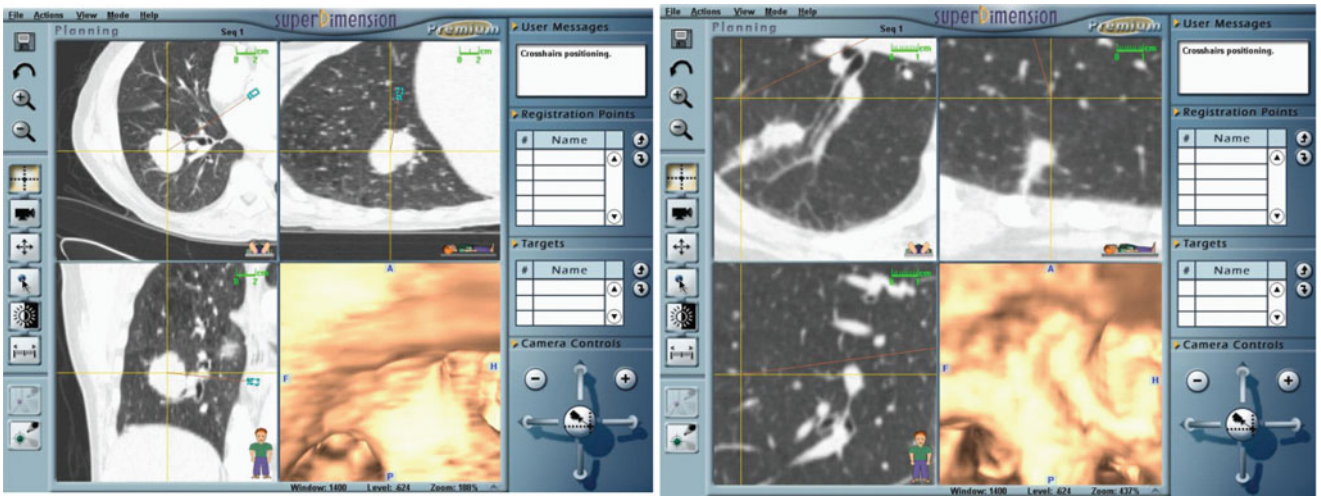

Fig. 24.9 Type A lesion (*left*) and type B (*right*)

registration error tends to increase as the lesion tends to be more peripheral. In addition, the system tends to be less accurate with lesions close to the diaphragm due to increase movement with the respiratory cycle.

A common differentiator for peripheral lesions is the division into type A lesions which have a bronchus leading directly to them and type B lesions, which do not (Fig. 24.9). Not surprisingly, Schwarz et al. have shown that diagnostic yields for transbronchial biopsy in type A lesions are greater than 77% while for type B, it is approximately 61%. In practice, biopsy is attempted in both type A and type B lesions with no specific guidelines at which distance is too far to attempt the procedure. Initially, there was some concern regarding the rate of iatrogenic pneumothorax associated with the procedure, but EMN bronchoscopy demonstrated to be safe; Eberhart et al. showed that in a study of 92 patients, there were only two small pneumothoraces, neither of which required intervention. It was further concluded that fluoroscopy was not required for the procedure to be performed safely.

EMN could guide physicians in the sampling mediastinal and hilar lymph nodes. Few retrospective studies reported on outcomes in the biopsy of mediastinal lymph nodes. It is important to note that due to paucity of literature on the role of EMN in lymph node sampling, the role of the technology in lung cancer staging is not as established as EBUS and is yet to be determined. There is conflicting evidence on a learning curve. Makris showed that there is no learning curve. Bansal reported in a retrospective analysis of procedures performed at their institution that that biopsies were obtained more successfully with practice.

The Veran SPiN Drive system uses a tableside navigation platform. In the initial planning stage, the patient must have a high-quality CT scan of the chest (there is no need for contrast material) with 0.62–1.25-mm cuts and 50% overlap. The later criteria provide adequate resolution for the system to create a 3D map of the airways and a virtual bronchoscopic view for appropriate navigation and guidance. It also provides cuts of the lung in coronal, sagittal, and longitudinal planes. The physician then marks the affected area to which navigation is desired (Fig. 24.10). The system suggests a pathway to the chosen target. Multiple targets can be marked at once, and multiple navigations can be performed. Once planning is performed, the chosen map is synched to the patient and navigation is performed. To compensate for respiratory variations, the system allows continuous adjustment through sensors placed on the patient chest. Navigation to the target is done by steering a 2-mm working channel with sensors on tip (Fig. 24.11). Steering is accomplished with a handheld controller similar to the flexible bronchoscope by following the delineated path displayed on the 3-dimentional tree, the virtual airway display, and the CT views all the way to the target. Once on target, position verification can be obtained as a virtual fluoroscopic view showing position, orientation, pathway, and target (Fig. 24.12).

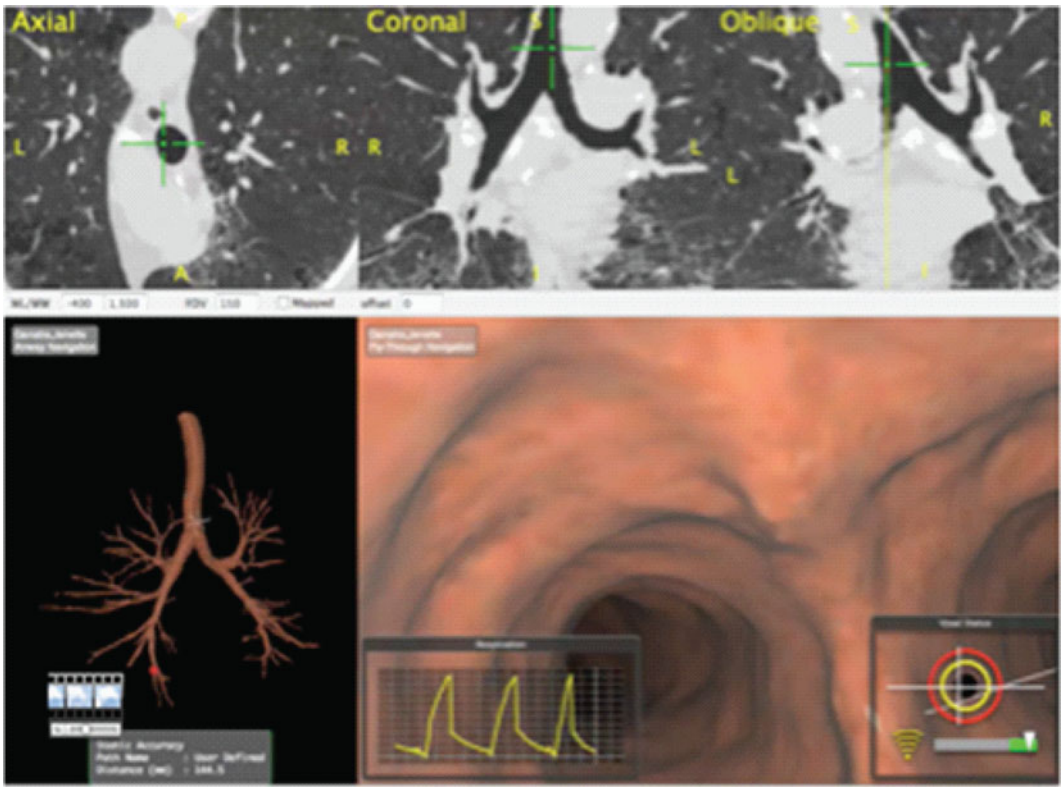

Fig. 24.10 Display the 3-D tree and CT views during navigation

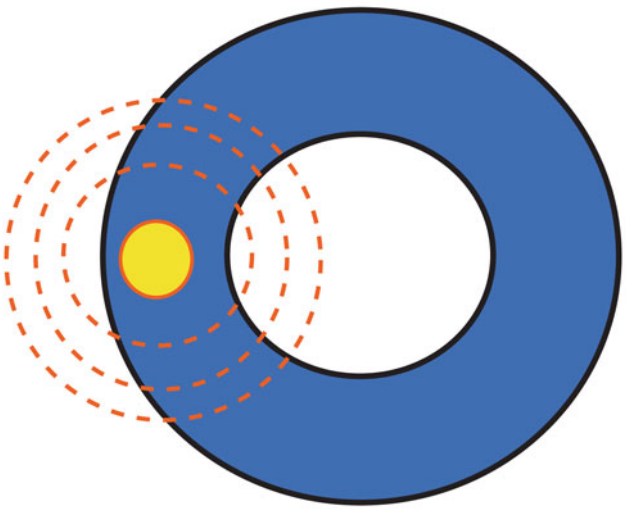

Fig. 24.11 Working channel (*blue*) and position sensor embedded in tip (*yellow dot*)

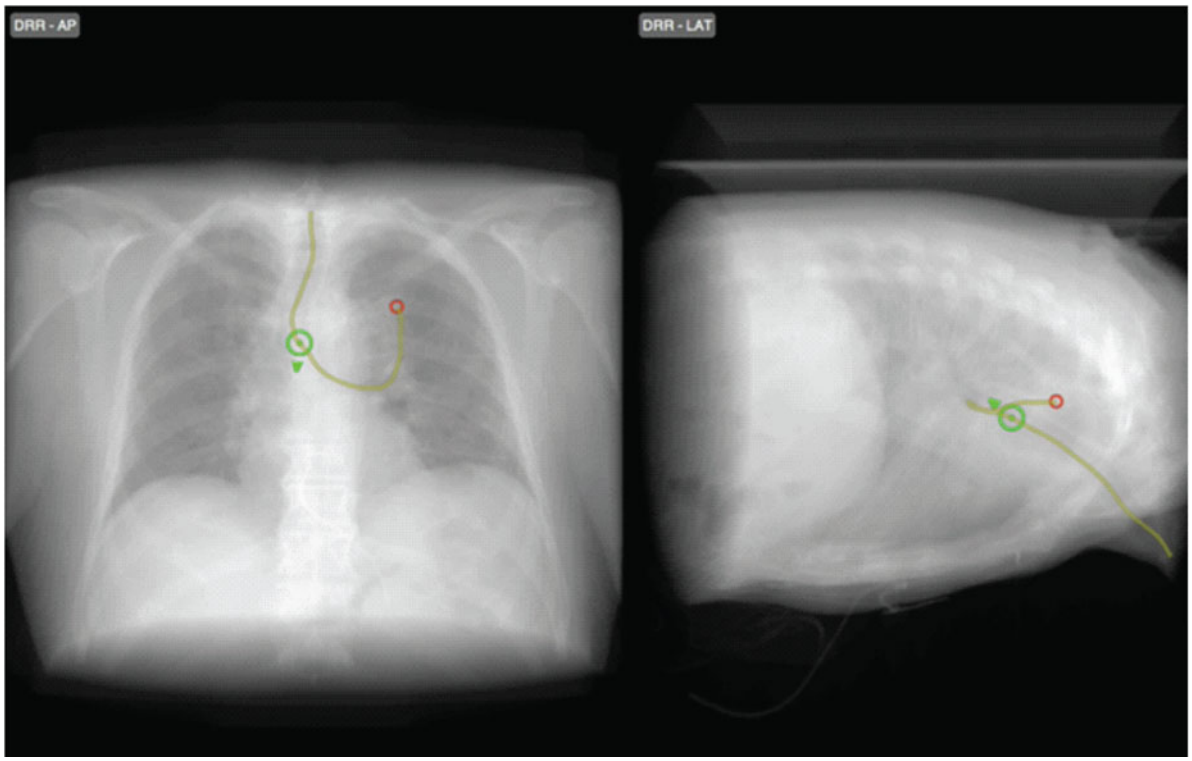

Fig. 24.12 Constructed fluoroscopic view showing real position (*green*), target(*red*), and pathway (*line*)

Currently, the Veran system's safety, accuracy, and diagnostic yield are being tested in selected centers. Data is not currently published.

Conclusion

Image-guided bronchoscopy is a method for the guidance of a bronchoscope to peripheral lesions. The technology is based on either virtual images synchronization or electromagnetic navigation. Studies show that the bronchoscopist can be guided to the target in a short time. To confirm location, additional methods are still in use in conjunction to image guidance; these include fluoroscopy and/or radial ultrasound. Using image guidance, data suggest greater yield and fewer complications when compared to standard transbronchial biopsy methods using only fluoroscopy. Importantly, with the advent of new endoscopic therapeutic nonsurgical modalities, accurate navigation and reach to peripheral lesion becomes critical. Image guidance and target identification plays an important role in thoracoscopic resection of peripheral nodules, placement of markers for radiosurgery, and placement of catheters for brachytherapy. Taken together, image-guided bronchoscopy plays an important diagnostic and potentially therapeutic role. Its widespread use is likely by pulmonologists and thoracic surgeons.

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Part III

Bronchoscopy, Section 2: Therapeutic Interventions

Malignant Central Airway Obstruction

25

Gaëtane Michaud

Definition and Presentation

Malignant central airway obstruction is broadly defined as obstruction of the trachea, either main stem bronchus and/or the bronchus intermedius by tumor. Generally, the airway must be obstructed at least 50 % prior to the development of symptoms; however, any other airway compromise such as bleeding, secretions, or edema may result in the patient becoming symptomatic with a lower-grade stenosis. Considering the average normal airway diameter of 12–18, 10–16, and 8–14 mm for the trachea, right and left main stem bronchi, respectively, a tracheal luminal diameter of less than 8 mm will result in exertional dyspnea and less than 5 mm rest symptoms. In many cases, the dyspnea is multifactorial as a large proportion of these patients will have concomitant chronic obstructive pulmonary disease, pleural effusions, or venous thromboembolic disease. There may be a reduction in surface area in the case of large mass lesions. In other cases, a ball-valve phenomenon can exist whereby gas trapping results in mechanical disadvantage increasing the work of breathing. Often patients will reduce their activity to avoid becoming short of breath and then slowly decondition. Of those patients presenting acutely with malignant airway obstructions, over half present in respiratory failure requiring emergent airway intervention. Other frequent presenting signs and symptoms include cough, wheezing, stridor, and recurrent or persistent post-obstructive pneumonia. Stridor is usually attributable to impingement at the level of trachea or larynx, whereas wheezing may be focal and as a result of obstruction distal to the main carina.

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Prevalence

The exact prevalence of central airway obstruction is unknown, although approximately 80,000 cases of malignant airway obstruction are treated annually in the United States. Nearly 1/3 of patients with non-small cell lung cancer are found to have malignant obstruction at presentation. Lung cancer recently became the leading cause of cancer death in both men and women in the United States. With the rising number of lung cancer cases, it is likely that this number will continue to increase. In addition, a wide range of other malignancies such as hematologic malignancies and solid organ tumors tend to either metastasize to the airways or mediastinal and/or hilar lymph nodes.

Etiology

Primary tracheal tumors are relatively rare and often unresectable. The vast majority in large series are squamous cell carcinomas, adenoid cystic carcinomas, carcinoids, mucoepidermoid tumors, and adenocarcinomas. The central airways are a common site of metastatic involvement from distant sites. Nearly any tumor can extend to the airway via hematogenous spread; however, those with the most affinity for the central airways include tumors of the aero-digestive tract, breast, renal cell carcinoma, and metastatic melanoma. As both the later two have a strong propensity to bleed, they may be particularly problematic and often require endobronchial management to avoid sequelae such as massive hemoptysis. A comprehensive list of tumors affecting the central airways can be found in Table 25.1.

Growth of tumors adjacent to the central airways or as a result of mediastinal lymphadenopathy may also result in obstruction due to simple mass effect. Esophageal cancers may extrinsically compress and in some cases erode into the trachea or main stem bronchi (most often the left main stem

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Table 25.1 Tumors affecting the central airways

Primary airway tumors	Metastases
Primary tracheal carcinoma	Bronchogenic
Adenoid cystic carcinoma	Renal cell carcinoma
Carcinoid	Metastatic melanoma
Mucoepidermoid tumor	Breast
Chondrosarcoma	Thyroid
Bronchogenic carcinomas	Prostate
Esophageal cancer	Sarcoma
Thyroid cancer	Lymphoma

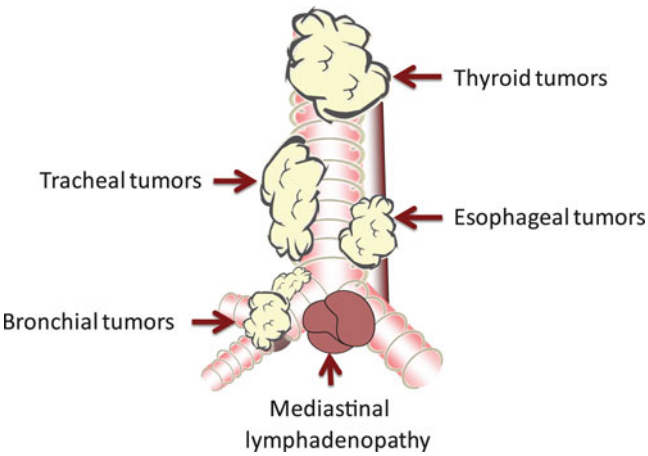

Fig. 25.1 Tumor-airway spatial relationships. The location of the airway mass may be suggestive of its etiology. The figure is a graph representation of typical locations of airway tumor involvement

bronchus) causing a malignant fistula. Thyroid cancers can also result in significant compression of the proximal airways, most often at the level of the extra-thoracic trachea. Lymphomas and other primary tumors that metastasize to the lungs may cause significant extrinsic compression at the level of the lower paratracheal or subcarinal lymph nodes leading to marked reduction in the luminal diameter of the distal trachea and/or main stem bronchi. Figure 25.1 provides a graphic representation of the tumor-airway spatial relationships potentially resulting in malignant central airway obstruction.

Classification

Central airway obstruction is generally classified into three categories depending on whether the tumor is purely endoluminal, extraluminal, or mixed. If the tumor is confined to the airway lumen (endoluminal), it is considered "intrinsic" compression. On the other hand, if the tumor is obstructing the airway due to mass effect and there is no endoluminal component, it is called "extrinsic" compression (extraluminal). The majority of central airway obstruction falls into the final "mixed" category, being that there are elements of both intrinsic and extrinsic involvement. With respect to the "mixed" category, the tumor often originates adjacent to the airway and erodes through the airway wall invading the lumen. This classification is quite important as it may impact on the therapeutic approach as discussed later in this chapter. Refer to Fig. 25.2 for a graphic representation of the three categories of airway tumor involvement.

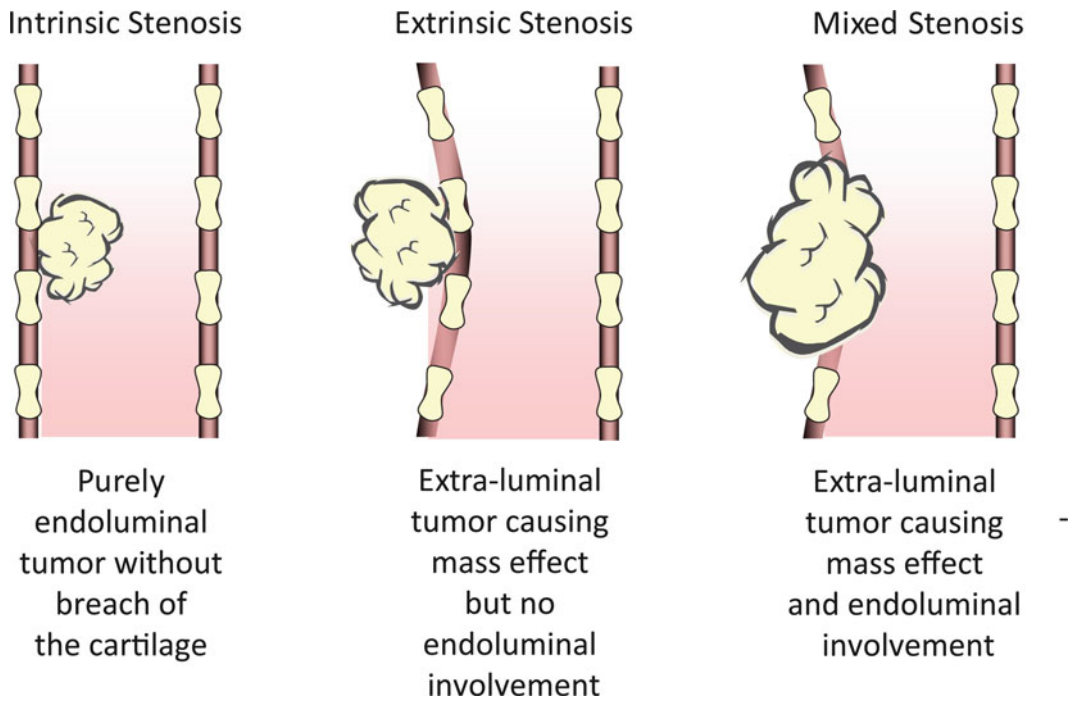

Fig. 25.2 Classification of airway tumor involvement. Tumor involvement in the airway is classified as intrinsic, extrinsic, or mixed based on whether the tumor is limited to the airway lumen, extra-luminal, or a combination of endoluminal and extra-luminal involvement, respectively

Diagnostic Approach

The diagnosis of malignant airway involvement may be delayed as the signs and symptoms can be quite nonspecific. These patients have frequently benefited from several courses of antibiotics prior to evaluation. Clinicians should have a low threshold to consider malignancy in high-risk patients, i.e., those with a prior or current diagnosis, strong family history of cancer, and exposure to known carcinogens such as tobacco or radiation. A comprehensive history and physical examination is necessary to determine the most appropriate diagnostic and staging evaluation. The clinical findings can also establish the urgency to intervene as well as provide information regarding special precautions necessary during the procedure.

With respect to diagnostic tests, a chest x-ray is often available; however, its utility in the management of these patients may be quite limited. Often, the airways are poorly visualized and this imaging technique provides scant information regarding the extent of the disease. The major value of the plain radiograph lies in its ability to provide information regarding the natural history of the tumor. In the case of atelectasis/lung collapse downstream from an obstruction, a longer duration of atelectasis renders the patient less likely to benefit from an airway intervention. Prior radiographs may provide some insight into the time course of the disease and likelihood of response to intervention but will add little to the actual treatment planning.

On the other hand, computed tomography (CT) can be quite helpful in that it may provide information regarding invasion by the tumor into the airways and mediastinal structures. The orientation of vascular structures as well as their patency also can provide valuable information for treatment planning. A CT scan, particularly with three-dimensional reconstructions, may help with decisions regarding selection of debridement technique and/or prostheses such as stents.

The ability to perform functional testing depends on the initial presentation. Spirometry may provide valuable information regarding both the severity and location, albeit intrathoracic or extra-thoracic. The spirometric abnormalities fall into three categories: (1) fixed airway obstruction with reductions of both inspiratory and expiratory flow rates and a box-like shape on the flow-volume loop, (2) variable intrathoracic obstruction with flow limitation on expiration and a reduction in the effort-dependent portion of the expiratory loop, and (3) variable extra-thoracic that shows reduction in the effort-dependent portion of the inspiratory limb of the flow-volume loop resulting from an inspiratory flow limitation. Despite concerns regarding the stability of these patients, Tremblay and colleagues recently showed that bedside spirometry may be safely performed in the majority of these patients and that marked post-procedure changes could be demonstrated which correlate with improvements in measures of quality of life.

Rigid Versus Flexible Bronchoscopy

The gold standard of diagnostic testing for malignant airway obstruction is bronchoscopy. The safety and efficacy of rigid versus flexible bronchoscopy as an initial tool remains controversial. The risks of flexible bronchoscopy without the ability to perform rigid bronchoscopy are many. Certainly in an already compromised airway, the major concern is that of destabilizing the already compensating patient by further limiting airflow. The bronchoscope itself may further limit the lumen and any airway trauma result in bleeding or edema aggravating the situation. A standard adult therapeutic bronchoscope may significantly reduce the ability to ventilate even through an endotracheal tube depending on the caliber of the tube. Another aspect to consider when selecting either flexible versus rigid bronchoscopy in the initial diagnostic approach is that of moderate sedation. Anesthesia for rigid bronchoscopy will be addressed separately. Commonly employed agents for moderate sedation include benzodiazepines and narcotics such as fentanyl. These sedatives may depress ventilation and relax respiratory musculature both of which may compromise the airway to a greater degree.

There are many advantages to the rigid bronchoscope in this setting are many. The major advantage is the ability to ventilate the patient while reestablishing airway patency. The rigid bronchoscope may also be used to tamponade any bleeding, selectively intubate one of the main stem bronchi, and/or mechanically debride the airway. The flexible bronchoscope may be used through the rigid barrel allowing for the evaluation of airways distal to the obstruction, particularly if using a smaller borescope such as the ultrathin bronchoscope. The flexible scope may be used to classify the lesion as intrinsic, extrinsic, or mixed obstruction; determine whether there are indeed airways beyond the obstruction; and measure the length of lesion. Unfortunately, the utility of the flexible bronchoscope to perform pulmonary toilet in the case of inspissated secretions distal to an obstruction may be limited by the caliber of the working channel.

Initial Airway Stabilization

The airway often requires initial stabilization as a bridge to definitive management. A very simple maneuver is to ensure optimal positioning of the patient to enhance pulmonary mechanics. Patients should be seated, rather than in the supine position. This may help on two fronts: first of all, it may help relieve any additional mass effect on the trachea, and secondly it may render respiratory muscle function more efficient. Supplemental oxygen should be applied via nasal cannulae or mask; however, often oxygenation does not appear to be problematic. Most frequently the major issue is that of turbulent airflow resulting from the obstruction. Turbulent flow is less efficient than laminar flow and may manifest clinically as

increased work during breathing. Helium's density is approximately 1/3 that of oxygen, resulting in a reduction in Reynold's number and an increased tendency for more laminar flow. Laminar flow produces less resistance than turbulent flow, and therefore, there is more flow for a given driving pressure. In order to optimize the flow characteristics, combinations of helium(70–80 %) and oxygen (20–30 %), called Heliox, may be administered. In patients requiring a higher fraction of oxygen, Heliox may not be appropriate. Patients with significant airway obstruction frequently have little reserve, and therefore, it is very important not to delay optimizing the oxygenation and airflow characteristics until the patient desaturates or deteriorates clinically.

Patient Selection for Airway Interventions

No literature exists regarding patient selection for airway interventions. In practice, most would agree that the patient should be symptomatic and that the symptoms are attributable to the airway obstruction. In select cases, airway interventions are considered prior to the onset of symptoms, especially if the procedure is also being performed for diagnostic or staging purposes. Endoscopic evaluation of the airway can help with staging and disease extent is often much more reliably determined based on bronchoscopic evaluation as compared to imaging. Endoscopic staging techniques include simple white light imaging to determine the tumor origin and proximity or involvement of the main carina. In addition, white light bronchoscopy may reveal previously undetected contralateral tumor involvement. Adjuncts to white light bronchoscopy that may add to the sensitivity to detect disease extent include autofluorescence bronchoscopy, narrowband imaging, or alternatively endobronchial ultrasound. Both autofluorescence bronchoscopy and narrowband imaging are techniques whereby wavelengths of light are utilized to determine the characteristics of the tissue. Detection of increased vascularity or changes in absorption/reflection characteristics may be suggestive of disease extension beyond the limits of the endoscopic abnormalities detected by white light bronchoscopy. With respect to endobronchial ultrasound, it may be useful in some cases to determine whether or not there is invasion of the airway. The endobronchial ultrasound may demonstrate that the tumor is confined to the lumen of the airway and is not invading through the cartilage. In this case, the patient may be amenable to endoscopic curative treatment particularly if a poor surgical candidate. Alternatively, the tumor may be completely outside of the airway and simply pushing on the airway. This again may influence the surgeons with respect to their surgical approach. In the case of esophageal or thyroid tumors, the fact that the tumor does not invade the airway but rather compresses may obviate the need for tracheal resection.

Evidence of distal airway patency and/or blood flow is preferable as there is a risk of worsening ventilation-perfusion matching if airway patency is reestablished despite lack of regional blood flow. This may be difficult to determine as there may be hypoxic vasoconstriction, which resolves once the airway is patent. Standard diagnostic tests such as ventilation-perfusion scans fail to identify patients at a higher probability of benefiting from airway intervention. A vascular cutoff sign may suggest a worse outcome of airway tumor debulking. If there is radiographic evidence of atelectasis/collapse distal to the obstruction that has been documented for a protracted period, i.e., several months, there is a lower likelihood of lung re-expansion post-procedure. Although there is no set point beyond which intervention should not be considered, the lung being down for a period of less than 30 days seems to portend a better outcome. If the patient is a candidate for curative intent management in a timely fashion, it may be best to limit interventions to those with potential to improve his/her chance of response to treatment. Examples could include debridement to determine tumor extent and operability or to allow for drainage in post-obstructive pneumonia prior to initiation of chemotherapy and/or radiation. Interestingly, patients initially thought not to be candidates for curative intent therapy may be found to actually be candidates for surgery. For example, tumors emanating from the upper lobes have a propensity to grow into and obstruct the main bronchi and bronchus intermedius or lower lobe. Following endoscopic resection, the tumor origin may be identified, and the bronchoscopist determines whether the tumor is confined to the upper lobe or extends into other lobes. The final consideration is that of life expectancy. Patients destined not to survive for a period sufficient to gain benefit from the intervention should be deferred. Just because you are technically able to open an airway does not necessarily mean it will benefit the patient, and in fact, it is essential to balance the potential risks and benefits of intervention of every case.

Anesthesia for Endoscopic Management of Malignant Airway Obstruction

Anesthesia for rigid bronchoscopy requires close collaboration and effective communication between the endoscopist and anesthetist. The majority of these procedures are performed in patients with comorbidities who are considered at high risk of adverse outcomes but for whom alternative less risky options do not exist. Most of these patients are classified by the American Society of Anesthesiologists (ASA) physical status classification of III-IV. In other words, they have severe systemic disease that may be a risk to life. In addition, many of these cases have a modifier to account for the prognostic impact of the urgency of the case.

General Treatment Principles by Classification of Stenosis

The most appropriate endobronchial management of a malignant airway stenosis is based on whether there is intrinsic, extrinsic, or mixed stenosis (Fig. 25.2). Purely intrinsic tumor involving the airway may simply be debrided and definitive management planned. If there is concern about rapid regrowth of tumor pending response to treatment, a stent may be considered (Figs. 25.3 and 25.4). Extrinsic airway compression nearly always results in recurrence within days to weeks if the airway is not stented following dilatation (Figs. 25.5 and 25.6). As such, the majority of these cases will require airway stenting to prevent recurrence pending initiation of definitive treatment. When there is a significant component of extrinsic compression as is often the case with mixed stenosis, simply removing the endoluminal component is insufficient to maintain airway patency while awaiting response to treatment. A stent may be necessary both to prevent regrowth and to counteract the mass effect of the extrinsic component.

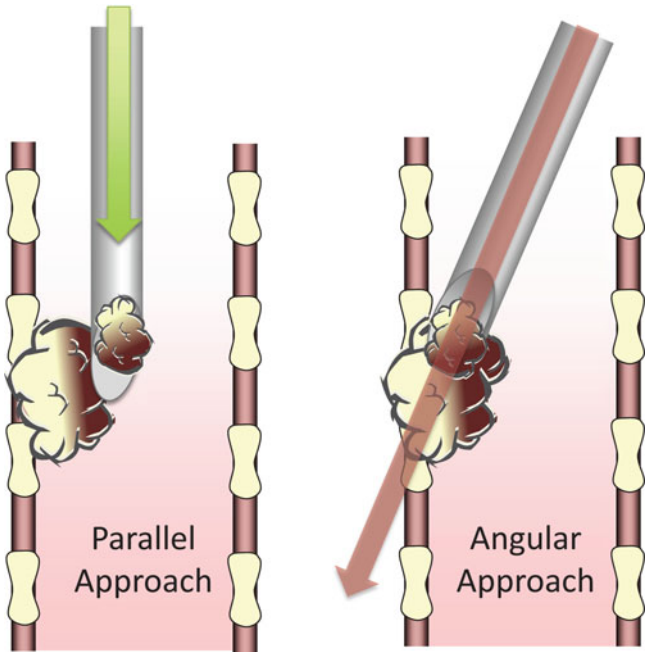

Fig. 25.3 Intrinsic airway obstruction pretreatment. Endoscopic view of left lower lobe of a patient with intrinsic compression related to endobronchial carcinoid

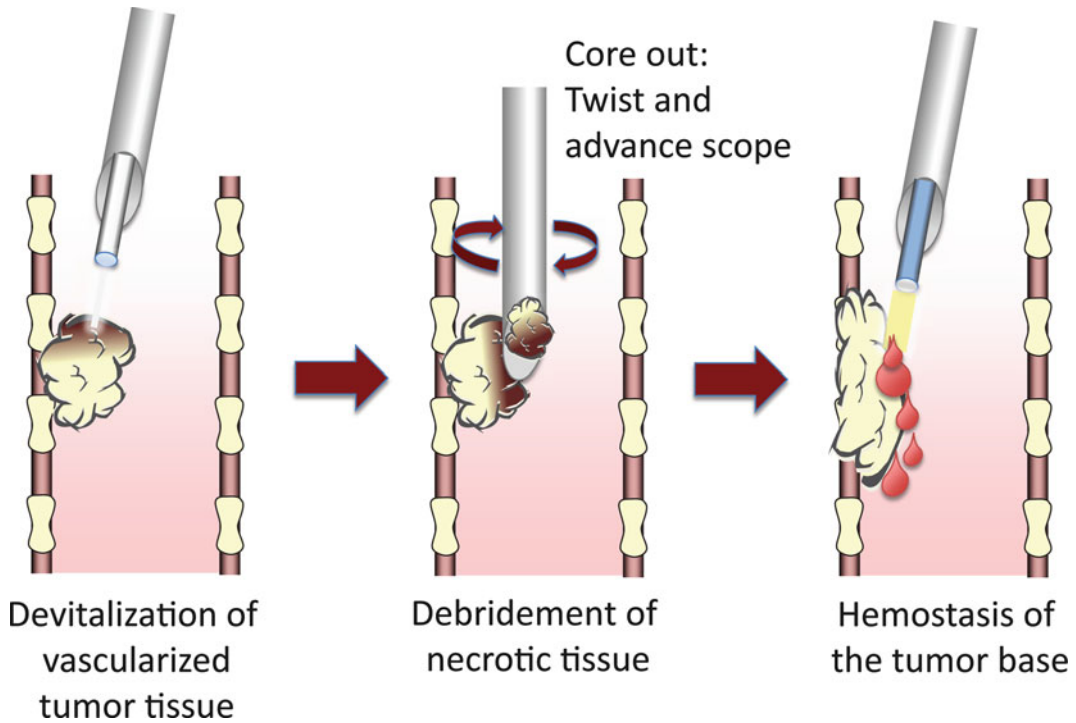

Fig. 25.4 Intrinsic airway compression following photodynamic therapy. Endoscopic view of left lower lobe of a patient with intrinsic compression related to endobronchial carcinoid upon completion of photodynamic therapy (PDT)

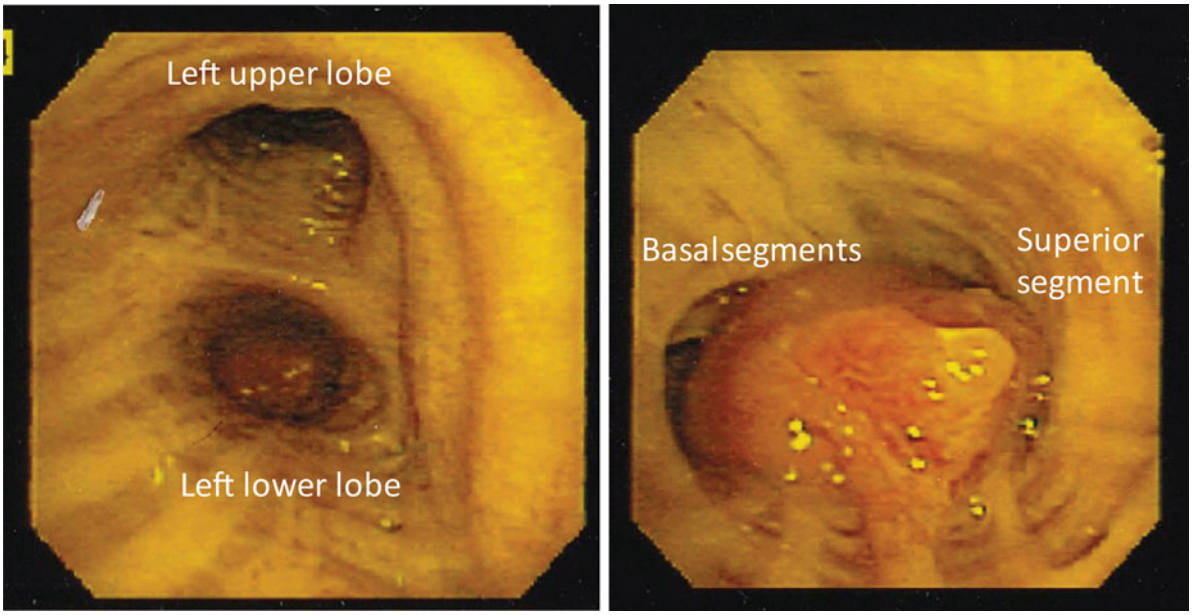

Fig. 25.5 Extrinsic airway compression. Endoscopic view of main carina and bronchus intermedius (BI) of a patient with extrinsic compression related to small cell lung cancer

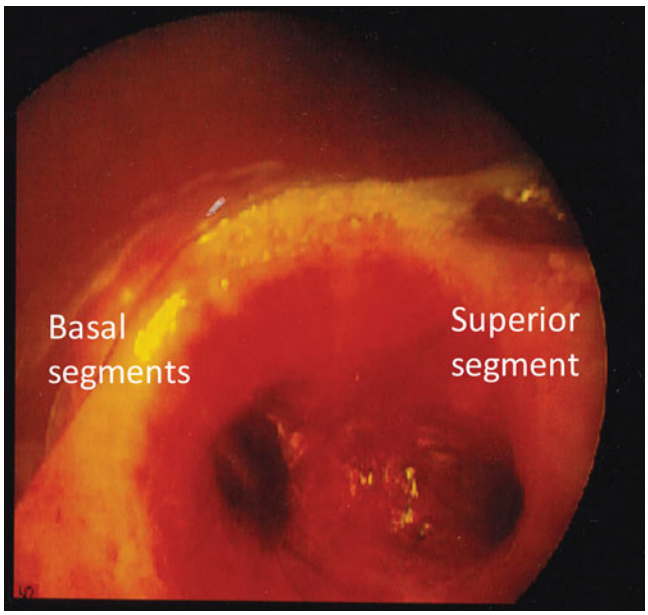

Fig. 25.6 Extrinsic airway compression following airway stent. Endoscopic view of main carina and bronchus intermedius (BI) following airway stenting

The most appropriate timing for endobronchial treatment remains controversial. In many cases, endobronchial therapy with relief of stenosis is necessary as stated above to be bridge to definitive management. In other words, it is performed to relieve symptoms pending more definitive treatment such as external beam radiation. In the case of highly chemo- or radiosensitive tumors such as small cell lung cancer, endobronchial management may be deferred until the patient demonstrates clinical relapse of their malignant airway obstruction. In addition, there are some concerns regarding potentiation of radiation effects in the context of metallic stents. The concern is that this may lead to perforation of the airway following radiotherapy. The ideal timing of endoscopic intervention is the subject of ongoing research.

Airway Dilation

The two main techniques used to dilate the airways in the context of malignant airway obstruction include balloon bronchoplasty and mechanical dilation with the rigid bronchoscope barrel. Although there are no designated balloons for airway dilation, many endoscopists perform airway balloon bronchoplasty using esophageal balloons of varying sizes. These balloons are filled with saline to achieve a preset airway diameter, and a constant pressure is applied to the airway for 30–60 seconds. Prolonged periods of balloon inflation should be avoided as it does not allow for ventilation distal to the balloon during inflation. When the trachea is dilated, the patient is apneic throughout balloon inflation. Overdistention of the balloon can result in airway rupture. This technique has been shown to successfully dilate the airways of patients with malignant airway obstruction in nearly 80 % of cases.

The rigid bronchoscope itself may also be used to dilate the airways. This works particularly well in the more proximal airways; however, the external diameter of the barrel may exceed the normal luminal dimensions of the smaller airways. Overdistention of the airways can lead to fracture of the cartilage. In order to minimize trauma to the larynx and avoid

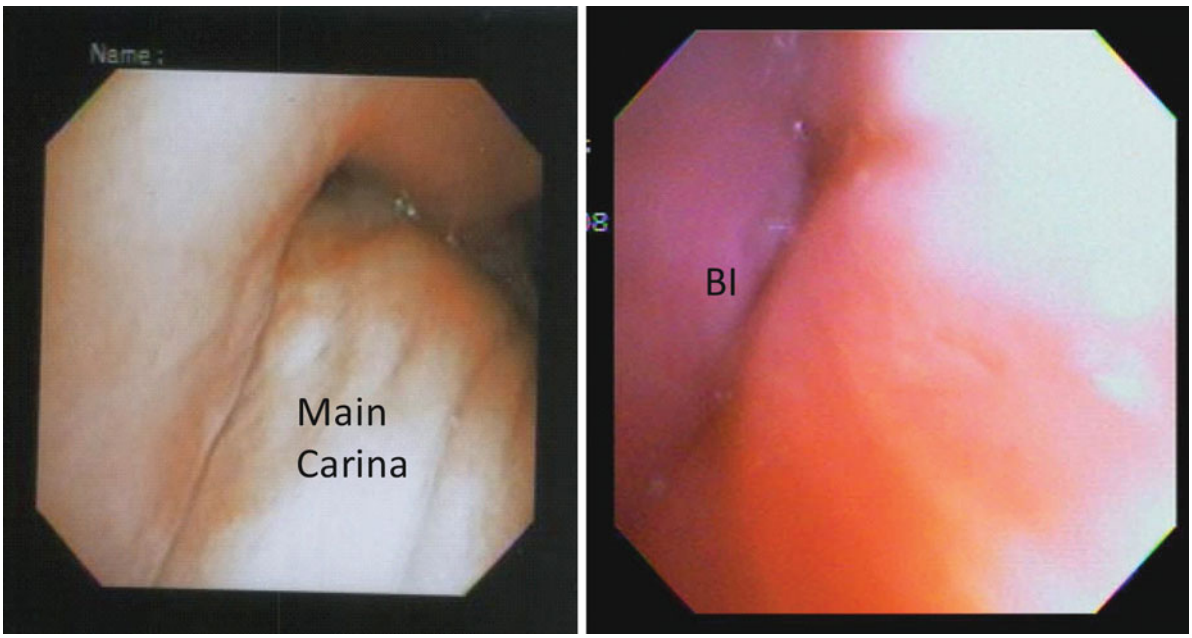

Fig. 25.7 Approach to mechanical debridement. When performing endobronchial tumor debulking, it is essential to remain within the axis of the airway to reduce the risk of airway perforation

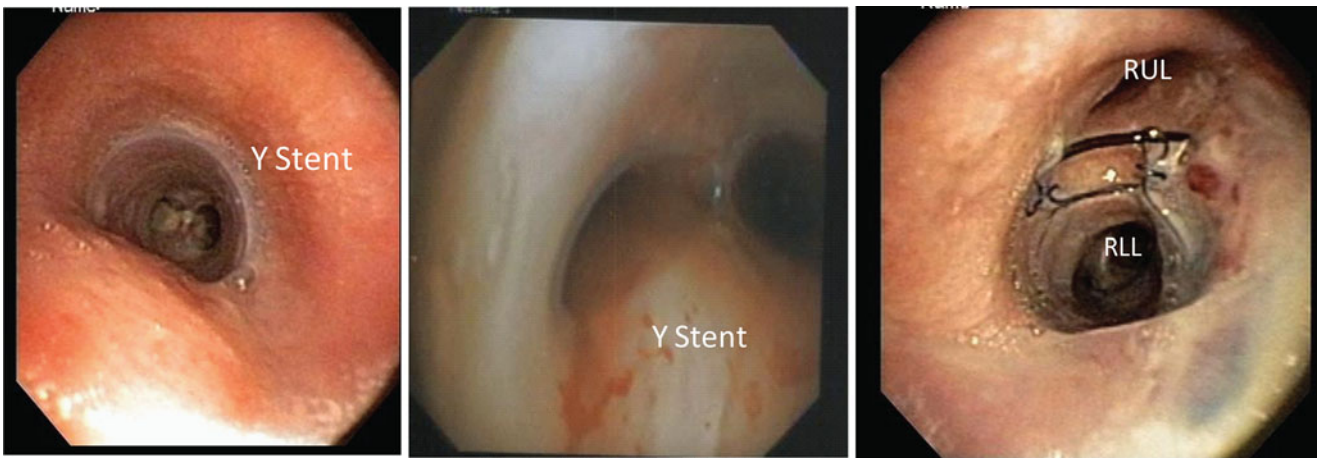

Fig. 25.8 Debridement technique. Airway tumor is devitalized using one of the many available techniques to reduce the risk of significant bleeding and then is mechanically debrided either with forceps or the bevel of the rigid bronchoscope. Finally, the base of the tumor is coagulated for further hemostasis

excess risk of loss of airway patency, the largest rigid tracheoscope accommodated by the trachea is first used to intubate the patient. Jet ventilation is initiated, and the patient is given several breaths. Next, the ventilation adapter is removed from the tracheoscope, and rigid bronchoscopes (longer with ventilation side ports) of increasing size are passed in sequence through the tracheoscope. After each bronchoscope is gently passed beyond the obstruction, it is left in place for several minutes so as to give the airway time to dilate and allow the patient to be ventilated. Once the largest bronchoscope able to fit through the tracheoscope has been successfully passed through the obstruction, the tracheoscope is twisted gently over the bronchoscope and past the obstruction. If the lesion is too distal, then the patient may need to be re-intubated with a large bronchoscope. The advantage to this technique over balloon bronchoplasty for more central lesions is that the patient can be ventilated throughout the procedure. In addition, during this process, the rigid barrel can be used to core out any intraluminal component of the tumor. It is essential to stay in the same plane as the native airway when performing mechanical debridement as more tangential orientation may result in airway perforation, as demonstrated in Fig. 25.7. The steps of airway debridement are depicted in Fig. 25.8.

The effects of dilation via either technique, balloon or rigid bronchoscope barrel, are immediate with obvious increase in the caliber of the lumen. Unfortunately, the results

of these techniques are often not sustained unless combined with debridement of intraluminal disease, or an airway stent is deployed to maintain the patency.

Tumor Ablative Techniques

Endobronchial tumor is often well vascularized with fragile vessels; therefore, prior to considering tumor debridement, it is often necessary to devitalize the tumor. A whole host of techniques exist to achieve the goal of devitalizing the tumor. Some of these have immediate effects, and therefore, airway patency can be achieved in a single procedure, whereas others are performed as staged procedures. Selection of the most appropriate adjunct depends on the stability of the patient, operator preference, and training as well as availability of equipment. In general, the sequence of events proceeds in a stepwise fashion. As shown in Fig. 25.8, the tumor is devascularized, necrotic tissue is excised from the airway wall, and then finally, hemostasis of the base is performed. The hemostasis step may also flatten the tumor base, which may help seat the stent when appropriate and reduce the rate of tumor regrowth. Multiple techniques exist for tumor ablation, these can broadly be categorized as those with an immediate versus a delayed action. The immediate ablative techniques include laser, electrocautery, and argon plasma coagulation, whereas the most common delayed techniques are cryotherapy, photodynamic therapy, and brachytherapy. Each of these modalities is discussed in depth within this volume. Please refer to the specific chapters.

In the majority of cases, ablative techniques are used for palliation of symptoms; however, in cases of slower growing tumors with less malignant potential such as typical carcinoids, there exists a body of literature showing curative potential with endoscopic treatment. Mechanical debulking of the tumor as described above is combined with treatment of the tumor base with photodynamic therapy, laser, electrocautery, brachytherapy, or cryotherapy. The potential for cure stems on the determination of whether or not the tumor is confined to the mucosa and fails to invade the airway cartilage. Even in slower growing tumors, one would only consider endobronchial therapy if the patient has contraindications to surgical management or if he/she refuses surgery.

Airway Stents

Once the airway has been debrided, the clinician must estimate the risk of airway re-collapse. If there is indeed a concern regarding post-procedure patency, then one may consider placement of an airway stent. Airway stents are the subject of a chapter within this text, and therefore, we refer you to this section for a comprehensive review of the topic.

Table 25.2 Stent comparison

Silicone	Metallic
Benign/malignant	Malignant only (?)
Removable	Difficult to remove
Rigid bronch only	Flex or rigid
Migration	Less migration
"Jail" adjacent bronchi	"Jail" only w/covered
Granulation tissue	Less granulation tissue
Retained secretions; mucus obstruction	Minimal retained secretions
Rigid – cannot conform	Expandable – conforms to airway
Inexpensive	Expensive

Complications related to stents may in and of themselves results in airway obstruction; these include migration, formation of granulation tissue, obstruction secondary to secretions, and bacterial overgrowth. Migration is most frequently the result of under-sizing the stent diameter or alternatively due to tumor involution secondary to treatment. This complication is rarely fatal and most often presents clinically as cough or dyspnea. It is managed simply by extraction of the migrated stent under rigid bronchoscopy and eventual replacement with a more appropriately sized stent. Migration occurs less frequently with metal stents than with silicone. Granulation tissue has a tendency to form at the proximal and distal margins of the stent and is related to chronic inflammation. They can lead to obstruction of the stent, and therefore, mechanical or thermal (laser, cautery, cryotherapy) means should be considered. Replacement of the stent may also be necessary. Metallic stents tend to generate more granulation tissue rendering them often quite difficult to remove, particularly when fractured. Mucoid impaction of the stent leading to obstruction may be quite serious and even lethal. These risks may be reduced by maintaining humidification of the stent via nebulization of sterile normal saline 2–3 times daily as well as regular use of mucolytics. Stents that become impacted with secretions (most often associated with bacterial overgrowth) should generally be removed and replaced.

Other considerations when selecting the most appropriate stent in malignant airway obstruction include operator skill, cost, and lesion conformation. The necessity for rigid bronchoscopy and general anesthesia for the placement of a silicone stent is considered by some as a disadvantage (Table 25.2). Due to pliability properties of the silicone stent, curvilinear conformations are not the ideal indication for silicone stents. In these situations, a silicone stent may either involute centrally resulting in obstruction or even migrate due to the tendency to maintain its straight tubular conformation. It is important to note that the cost of a silicone stent is 1.5-2 times less than a metal auto-expandable stent. Although

the ideal airway stent, suitable for all clinical situations, does not exist. In general airway stents for malignant indications provide effective palliation of symptoms attributable to central airway obstruction.

In summary, malignant central airway obstruction occurs during the course of disease in many cancers including NSCLC and other solid organ tumors. Most patients become symptomatic once a critical degree of stenosis ensues. Airway interventions such as tumor ablative techniques and airway stenting provide effective palliation for these patients beyond conventional treatments with chemotherapy and radiation. A variety of techniques are available with relatively equivalent efficacy, and the appropriate selection depends on local expertise, availability of necessary resources, and patient/physician preference with respect to side effect profile. With the growing availability of qualified physicians able to care for patients with complex airway diseases, it is likely that more of these patients will be recognized and treated endoscopically rather than pursuing palliative medical management alone (Fig. 25.9).

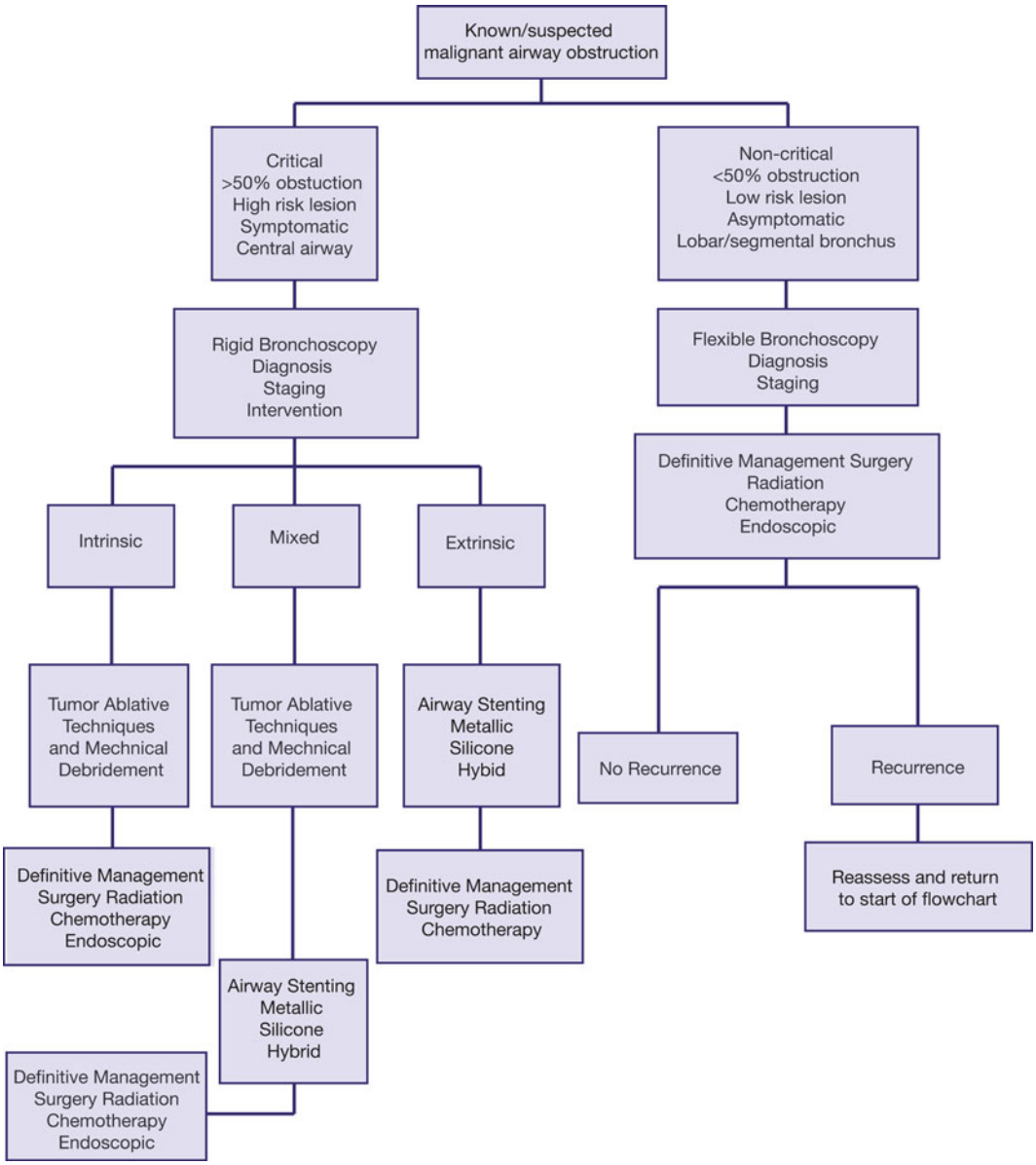

Fig. 25.9 Algorithm for the management of malignant airway obstruction. Patients evaluated with suspected or known malignant airway obstruction are initially classified as critical or non-critical stenoses. If deemed critical, a rigid bronchoscopy is performed for diagnosis, staging, and intervention. Tumor characteristics are identified, and treatment tailored to whether the tumor leads to intrinsic, mixed, or extrinsic airway obstruction. Patients found to have non-critical stenoses undergo flexible (and in some cases rigid) bronchoscopy for diagnosis and staging. Endoscopic treatment is deferred until patient demonstrates recurrence refractory for definitive treatments such as surgery, radiation, or chemotherapy

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Management Principles of Nonmalignant Airway Obstruction

26

Devanand Anantham

Introduction

Nonmalignant airway obstruction covers a broad scope of disparate pathologies (Table 26.1) that differ from malignant disease in both risk of complications and natural history. Tumors typically manifest with either endoluminal or extrinsic compression, while benign stenosis has a wider range of presentation that includes tracheomalacia and cicatricial scars as well. Malignant airway obstruction usually carries a dire prognosis that necessitates a palliative treatment plan. In contrast, the life expectancy with benign disease is usually not limited by the airway pathology. Therefore, curative options should be sought, and every patient evaluated for surgical resection or reconstruction by an experienced airway surgeon and team. Ill-advised endoscopic intervention such as stenting can inadvertently extend the stenosis through iatrogenic complications and hinder subsequent surgical repair. However, the expertise required for tracheal surgery from both surgeons and anesthetists is subspecialized and limited in availability around the world. In addition, surgical results are not guaranteed, and operative risks are not insignificant.

More than half of all the procedures in therapeutic bronchoscopy involve patients with benign airway disease, and nearly 40% are performed on an urgent or emergency basis. A third of all patients with benign pathology undergoing rigid endoscopy have an ECOG functional performance status score of >2. This need for urgent intervention in patients with impaired functional capacity, coupled with the necessity for subspecialized surgical expertise and the recent advancement of bronchoscopic techniques, has challenged the paradigm that nonmalignant airway obstruction should be managed primarily by surgeons. Furthermore, endoscopic treatments on benign disease carry a lower risk of short-term complications, as well as less intraoperative hypoxia and bleeding than similar procedures on patients with malignant pathology. The relationship between therapeutic bronchoscopy and tracheal surgery is in practice intertwined and complimentary. Outcome data are difficult to compare because surgical series often exclude inoperable patients while endoscopic studies focus on only such inoperable cases. There is also no single definitive treatment for any particular pathology or any absolute indication for any particular intervention. Despite the lack of consensus on the choice of definitive therapy, the management principles remain fairly straightforward.

The principles of treating nonmalignant airway obstruction are (1) stabilization of the patient, (2) thorough evaluation within a multidisciplinary context, and (3) careful selection of an appropriate intervention for each case (Fig. 26.1). Endoscopic therapy is often used to secure the airways, and bronchoscopic evaluation is pivotal in the selection of definitive treatment. Bronchoscopy also plays a big role in planning and preparing a patient for surgery. Furthermore, patients who may require specific systemic therapy for infections, connective tissue diseases, or inflammations can be identified. The choice of appropriate therapeutic intervention is determined by the unique characteristics and the benefits/risks of treatment modalities (Fig. 26.1). Disease parameters that include etiology, pathophysiology, natural history, and complicating factors such as malacia or laryngeal involvement also determine treatment outcomes.

Stabilization/Immediate Management

In respiratory distress, the airway must first be secured (Fig. 26.2). This is a basic principle of providing any emergency life support. No attempt should be made to push the endotracheal tube forcibly through a tracheal stricture. If a

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Table 26.1 Nonmalignant airway obstruction classified by type of stenosis

Type of stenosis	Pathology
Intraluminal	Inflammatory: Wegener's granulomatosis (systemic)
	Sarcoidosis
	Relapsing polychondritis (with malacia)
	Infections: endobronchial tuberculosis
	Aspergillosis
	Papillomatosis
	Hamartoma
	Hemangioma
	Tracheopathia osteoplastica
	Amyloidosis
	Pseudotumor
	Granulation tissue/granuloma
	Broncholith
	Foreign body
	Mucous plug
	Blood clot
Extrinsic compression	Lymphadenopathy
	Goiter
	Mediastinal cyst
Distortion	Vascular sling
	Post pneumonectomy syndrome
Scar/stricture	Post-intubation/tracheotomy stenosis
	Idiopathic subglottic/tracheal stenosis
	Fibrotic phase of infectious and inflammatory lesion
Anastomotic complications from tracheal surgery and lung transplant	Granulation tissue
	Fibrosis
	Bronchomalacia
	Necrosis/mucosal sloughing Infection
Dynamic airway obstruction	Tracheomalacia
	Bronchomalacia

small endotracheal tube cannot traverse the lesion, the tube should be placed just above the lesion and the airway suctioned adequately. Alternatively, a laryngeal mask or a tracheotomy may be needed. Rigid bronchoscopy can then be undertaken to evaluate the lesion and establish a more stable airway. Patients in respiratory distress may not be able to lie supine and often need to be managed in the upright position until anesthetic induction. Heliox which is blended helium (60–80%) and oxygen can be used as a bridge prior to securing the airway. Helium, which is less dense than nitrogen, provides more laminar flow past obstructions and reduces turbulence, as well as the work of breathing. Intravenous induction is preferred over inhalational induction because it is more rapid and does not irritate the airway. Neuromuscular blockade that may precipitate a loss of muscle tone and result in airway collapse especially in the presence of an anterior mediastinal mass is relatively contraindicated except in experienced hands. Intravenous dexamethasone and nebulized L-epinephrine have only been studied in the context of laryngeal edema and cannot be recommended for routine use because of inconclusive results.

Endotracheal intubation with rigid bronchoscopy not only secures the airway but also permits therapeutic interventions that can palliate the obstruction. The rigid barrel can be used for coring out intraluminal lesions or to sequentially dilate strictures. There is control of bleeding by direct tamponade, and other modalities such as mechanical debridement, lasers, or stents may be employed. In all these interventions, the anesthetist must always have priority in ventilating the patient, and, when requested, endoscopic therapy should temporarily cease and the patient ventilated.

Placement of a tracheotomy as a temporizing measure should be avoided where possible because tracheotomies can extend the stenosis and compromise the length of normal trachea available for surgical anastomosis. If a presurgical tracheotomy is indeed needed, it should be placed in the area of stenosis or at the site of any previous tracheotomy. Then both the stenosis and the new stoma can be resected together during subsequent tracheal surgery. Any temporizing tracheostomy tube must pass the entire length of the stricture to provide a secure airway.

Patients who are not in overt respiratory distress are managed by providing supplemental oxygen with humidification, intensive monitoring, gentle chest physiotherapy, and oropharyngeal suctioning. Nebulized saline, N-acetyl cysteine, and other agents to improve mucociliary clearance have been used, but they carry the risk of provoking bronchospasm (Fig. 26.2). Often, patients settle sufficiently with the gentle use of anxiolytics to enable a semi-elective bronchoscopic evaluation before definitive treatment can be instituted.

Evaluation

Clinical Evaluation

The clinical presentation is dependent on the severity of airway obstruction and on cardiopulmonary reserve. Typically, patients remain asymptomatic until stenosis exceeds 50%. Effort tolerance is first affected because the pressure drop across any obstruction increases with increasing airflow velocity. Symptoms at rest often only present when tracheal lumen narrowing is ≤5 mm. As a result of being relatively asymptomatic despite the presence of severe airway obstruction, these patients may only be first identified when a precipitant such as infection, edema, or mucous impaction triggers a life-threatening airway occlusion.

A high index of suspicion is needed if the patient presents with a history of prior endotracheal intubation or tracheotomy, tuberculous endobronchitis, gastroesophageal reflux

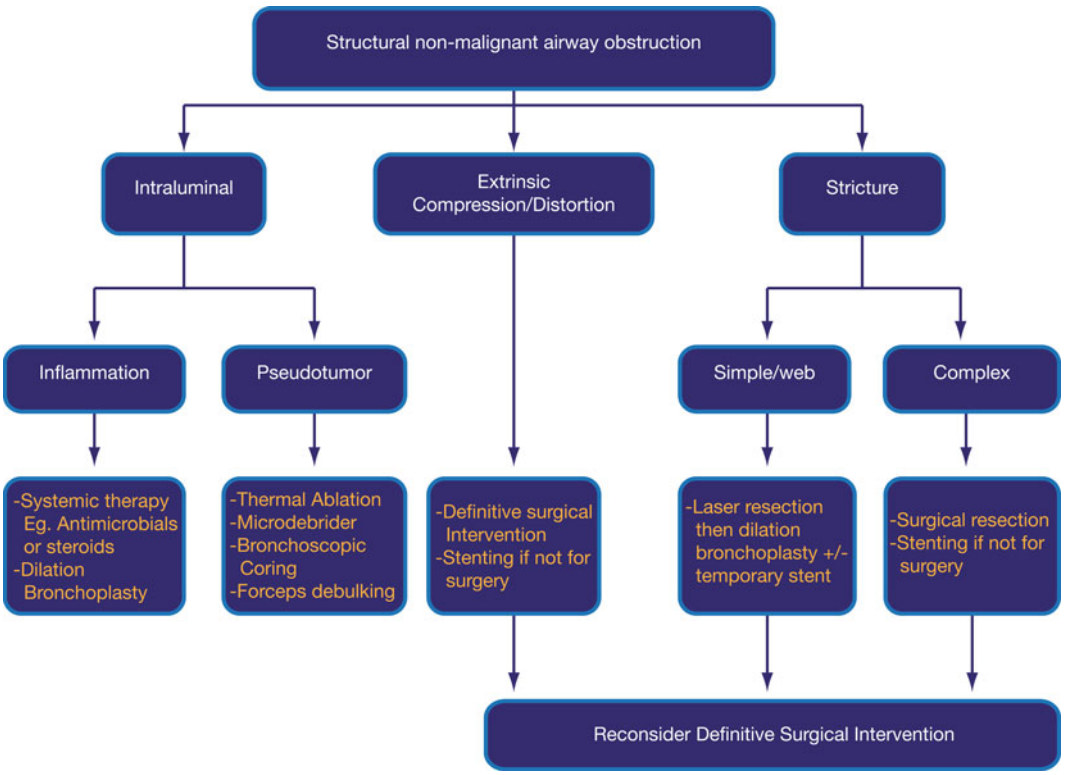

Fig. 26.1 Algorithm for the management of nonmalignant airway obstruction

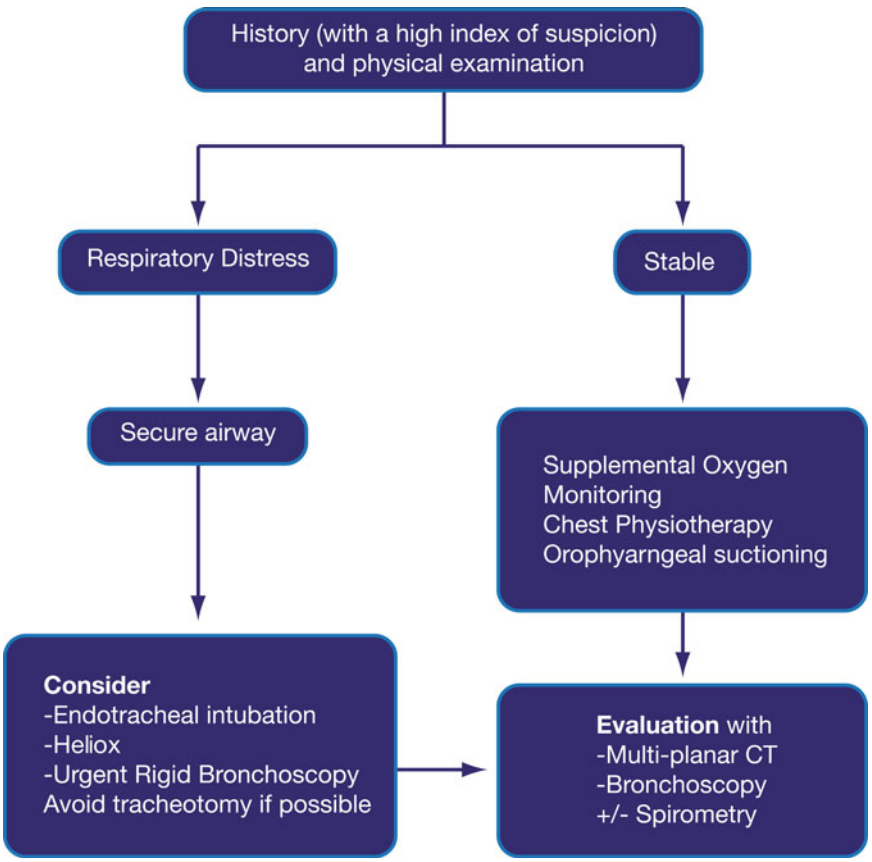

Fig. 26.2 Algorithm for the stabilization and evaluation of nonmalignant airway obstruction

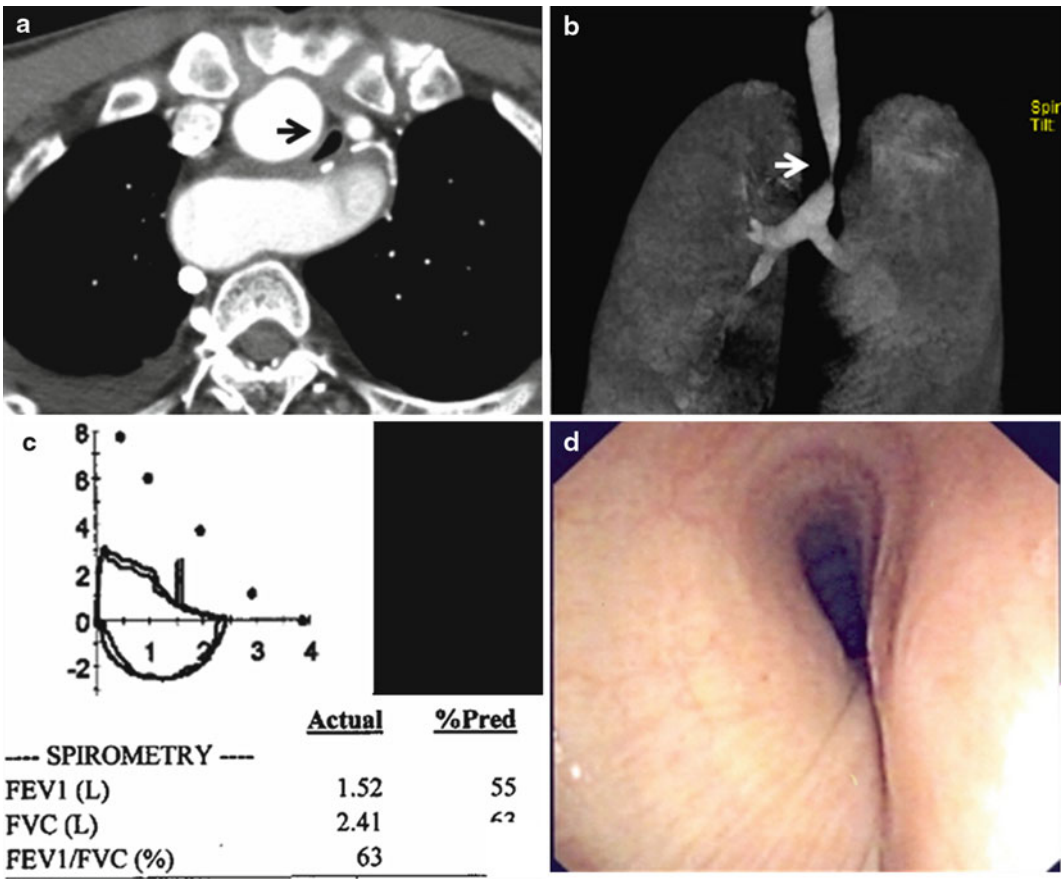

Fig. 26.3 Evaluation of airway stenosis with (**a**) computed tomography, (**b**) three-dimensional reconstruction imaging, (**c**) spirometry, and (**d**) flexible bronchoscopy showing a mid-tracheal extrinsic compression due to a vascular sling

disease, or systemic illnesses such as Wegener's granulomatosis or relapsing polychondritis. Wheezing refractory to bronchodilator therapy and recurrent pneumonia are classical presentations, and stridor or unilateral wheezing on physical examination is a clear indication for airway evaluation. Hypoxia or hypercapnia may not be present even in the presence of severe dyspnea.

Investigations

Computed tomography (CT) can provide valuable anatomical information on the location and extent of the lesion. However, standard axial imaging provides limited information on the length of obstruction, the relationship to adjacent mediastinal structures, and the presence of malacia. Therefore, multi-planar imaging with three-dimensional reconstruction and dynamic expiratory CT is preferred (Fig. 26.3).

Spirometry may yield classical flow-volume loop patterns of upper airway obstruction (Fig. 26.3), but sensitivity is low, and the typical flow loop cutoffs are not seen until the tracheal lumen is narrowed to <10 mm. Hence, normal spirometry does not rule out the diagnosis of airway obstruction in any patient in whom it is suspected and bronchoscopic evaluation is still warranted. Although there may be some role for spirometry in objectively documenting physiological severity of lesions, this evaluation can be confounded by obstructions at multiple sites and by comorbid airway disease such as chronic obstructive pulmonary disease (COPD). Furthermore, spirometry is a demanding investigation on patients who are in respiratory distress, and they are often unable to produce either satisfactory or reproducible measurements.

Bronchoscopic Evaluation

Bronchoscopy is the diagnostic modality of choice in all airway obstruction. However, the timing is debatable with some endoscopists recommending initial, routine flexible bronchoscopic evaluation of all referred cases as opposed to deferring airway inspection to the time of treatment with rigid endoscopy. Flexible bronchoscopy may be dangerous in patients with severe airway obstruction because the obstruction can be worsened by the bronchoscope physically

occluding the limited airway. However, this problem can be overcome in some cases by using ultrathin or pediatric scopes. Respiratory failure may also be exacerbated by moderate sedation. Therefore, any attempt at bronchoscopy must be undertaken in a setting with a skilled endoscopist, appropriate personnel, and facilities for advanced airway management including emergency tracheotomy. Any doubt about the ability to secure the airway should prompt evaluation with a rigid ventilating bronchoscope that has the advantage of enabling the endoscopist to concurrently control ventilation and examine the airways. Larger instrumentation is also possible with more options for therapeutic intervention, and flexible bronchoscopy can still be performed via the rigid barrel to examine the lobar and segmental airways.

Bronchoscopy enables detailed evaluation of lesions, patency assessment of airways distal to the obstruction, and examination of mucosa for evidence of active inflammation. Biopsies can be taken if the diagnosis is uncertain. However, bleeding from endobronchial biopsy, which is usually self-limiting, can in some instances exacerbate airway occlusion. Rigid bronchoscopy provides a safer option for the biopsy of central vascular lesions by securing the airway, offering superior suction capability, and enabling direct tamponade of any bleeding sites.

A standard classification system for airway obstruction has yet to be established, and this can prove a major hindrance to communication in a multidisciplinary team. One recently proposed system by Freitag et al. improves precision and interobserver agreement by classifying stenosis as either structural or dynamic and then further subdivides lesions by location, degree of stenosis, and transition zone. Although other staging systems of laryngotracheal stenosis have been previously devised and correspond with surgical outcomes, these systems are heavily weighted to the location of the lesion and are limited in application to only the upper trachea.

In the classification system, structural stenosis is classified into four groups: intraluminal occlusion, extrinsic compression, distortion, or scar (Fig. 26.4). Dynamic stenosis is defined by >50% airflow obstruction in expiration and is categorized as either cartilage malacia or a floppy posterior tracheal membrane (Fig. 26.5). Cartilage damage results in a saber-sheath trachea if the lateral walls are weak, a crescent-shaped trachea if the anterior walls are weak, and a circumferentially occluded trachea if both anterior and lateral walls are involved. In contrast, excessive dynamic airway collapse involves only the bulging of the floppy posterior wall. It typically involves the lower trachea and main stem bronchi. Endoscopic quantification of the degree of any dynamic stenosis needs to account for confounding variables such as patient position, depth of sedation, and the use of respiratory maneuvers in functional bronchoscopy.

The location of the pathology is described to be in the upper, middle, or lower third of the trachea or in either main stem bronchi (Fig. 26.6). The surgical implication is that up to half the upper and middle trachea can be resected, but the length of resection is limited to 40 mm at the level of the carina. Measurements in relation to normal airway landmarks such as the vocal cords, cricoid cartilage, carina, and major bronchial bifurcations provide greater accuracy in defining location. These measurements should be made from the top, as well as from the bottom of the lesion. A lesion is considered a simple stenosis if confined to a single cartilage ring without any associated malacia or chondritis. Complex stenoses are more extensive in length (Fig. 26.7) and are complicated by cartilage damage. They often have poorer results with endoscopic intervention.

The degree of endoluminal occlusion is categorized as <25%, 26–50%, 51–75%, 76–90%, and 90% to complete obstruction (Fig. 26.8). The severity is measured at its worst point in the respiratory cycle, and this usually occurs at the end of expiration. Transition zone refers to the abruptness of change of the airway obstruction which can be sudden as in web stenosis or more gradual and shaped like a bottleneck in cicatricial lesions (Fig. 26.9).

Laryngeal competence, involvement of the cricoid cartilage, presence of inflammation or malacia, and adequacy of distal airways should also be assessed during initial bronchoscopy. These factors will affect results with endoscopic intervention and may mandate an early surgical referral. Moreover, if a nonfunctional larynx is not recognized preoperatively, patients will need further tracheotomy or endotracheal intubation even after tracheal surgery. The technique of surgical management of subglottic stenosis (between vocal cords and lower border of cricoid cartilage) is different from the treatment of pure tracheal stenosis which makes identification of the cricoid cartilage in relation to the lesion essential. The cricoid cartilage lies proximal to the first tracheal ring and is the only complete cartilaginous band with no posterior muscular membrane (Fig. 26.10). Treatment results also improve if intervention occurs after airway inflammation has been allowed to resolve and the extent of the resultant scar clarified. Surgery is rarely indicated for inflammatory or infectious airway lesions because of the unpredictable natural history. Granulation, edema, and friable mucosa indicate inflammation, while pure fibrous lesions are completely covered with normal mucosa (Fig. 26.11). Temporizing solutions such as dilation can be sought to “buy” time for a stenosis to mature before proceeding with definitive intervention. The quality of distal airways for adequacy of surgical anastomosis is an obvious consideration of preoperative planning, and inspissated secretions distal to obstructions should be drained to avoid infection.

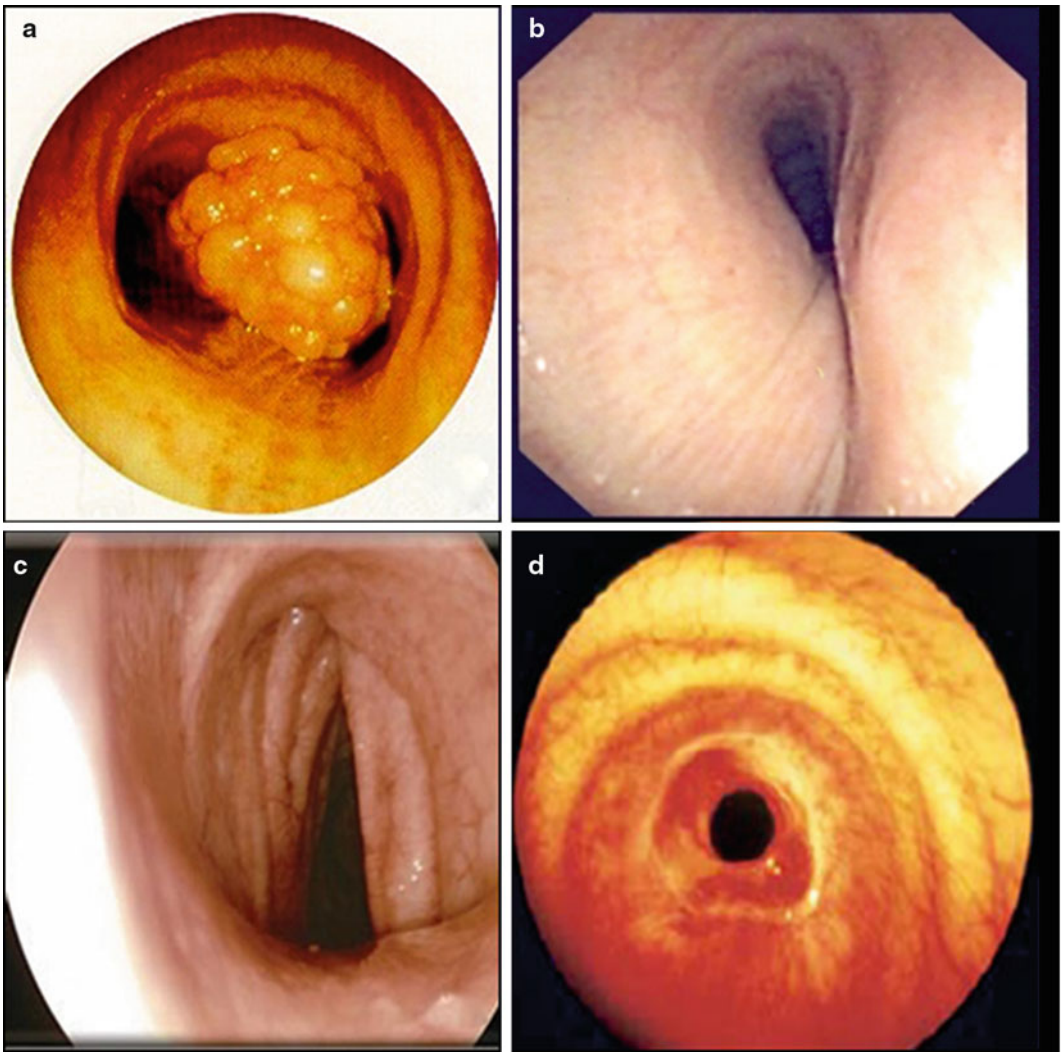

Fig. 26.4 Classification of structural airway stenosis: (**a**) intraluminal occlusion from papillomatosis, (**b**) extrinsic compression from a vascular sling, (**c**) distortion in an A-shaped post-tracheotomy stricture, and (**d**) scar from idiopathic tracheal stenosis

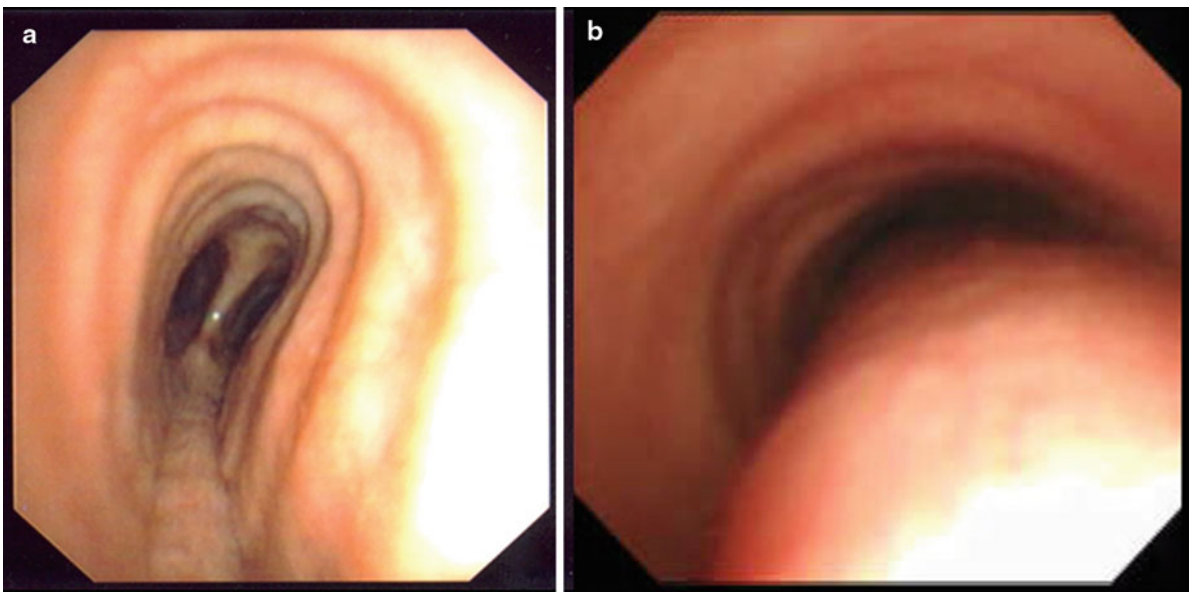

Fig. 26.5 Dynamic airway obstruction showing (**a**) saber-sheath trachea with lateral wall damage and (**b**) excessive dynamic airway collapse with a floppy posterior membrane

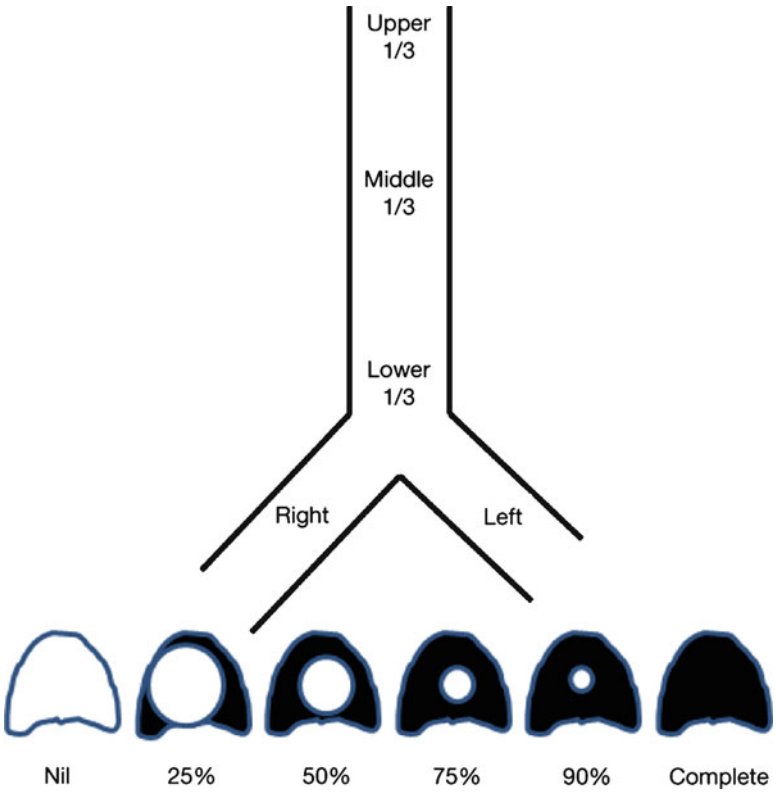

Fig. 26.6 Worksheet representation of location and degree of stenosis

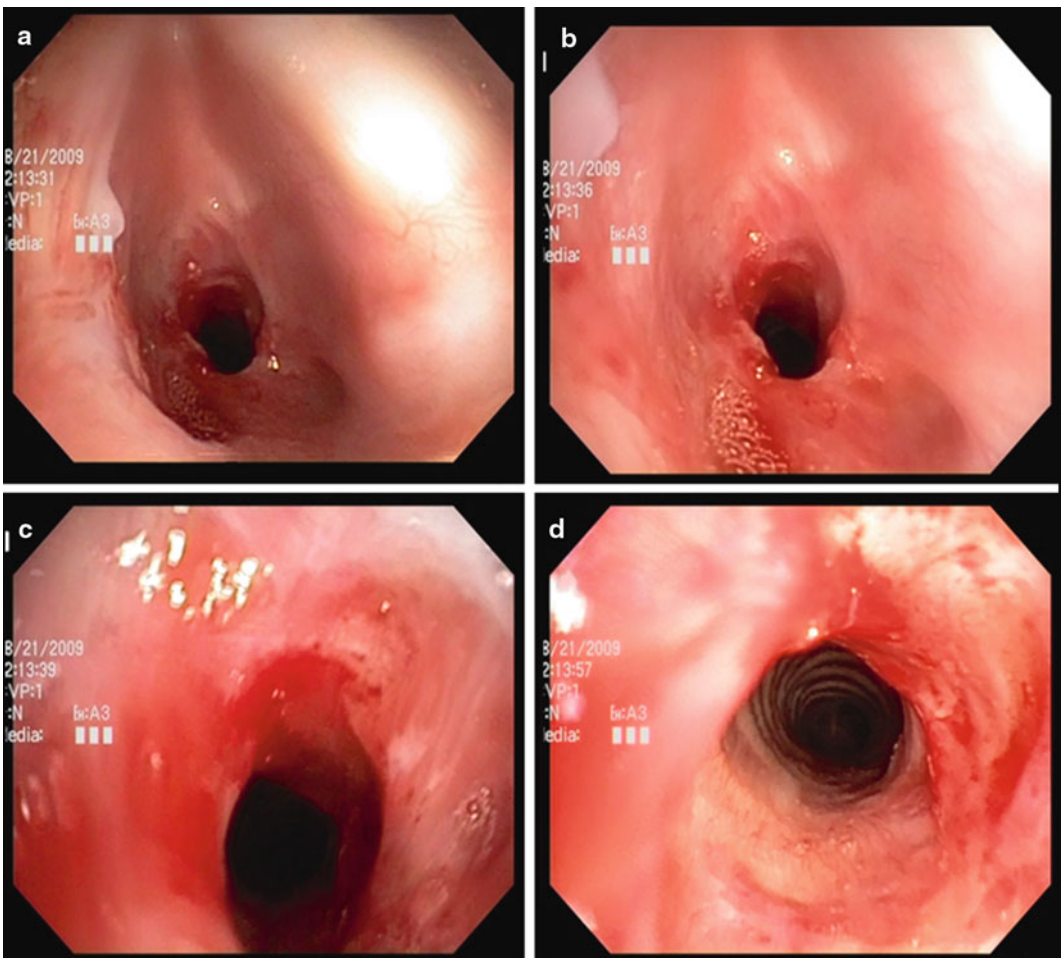

Fig. 26.7 Evaluating a complex subglottic stenosis moving from the proximal portion (**a**) of the lesion to the most distal portion (**d**)

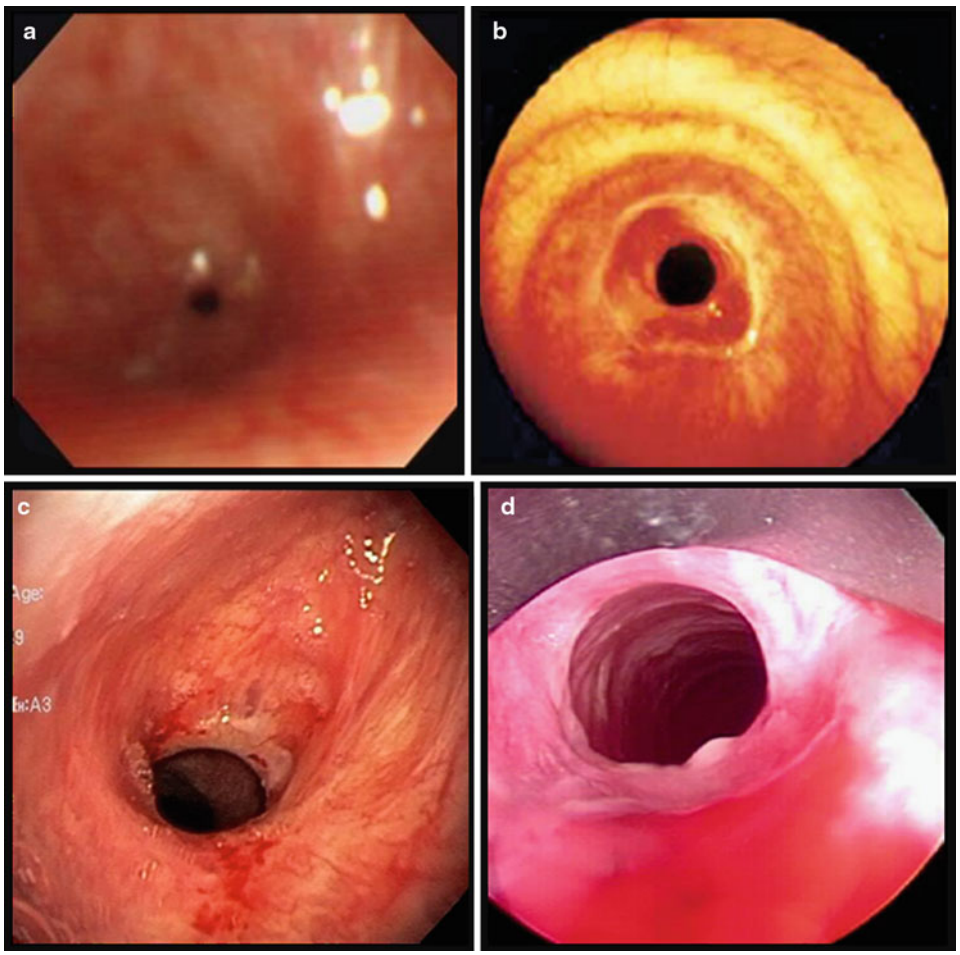

Fig. 26.8 The degree of endoluminal occlusion as visualized on flexible bronchoscopy as (**a**) 90%, (**b**) 75%, (**c**) 50%, and (**d**) 25%

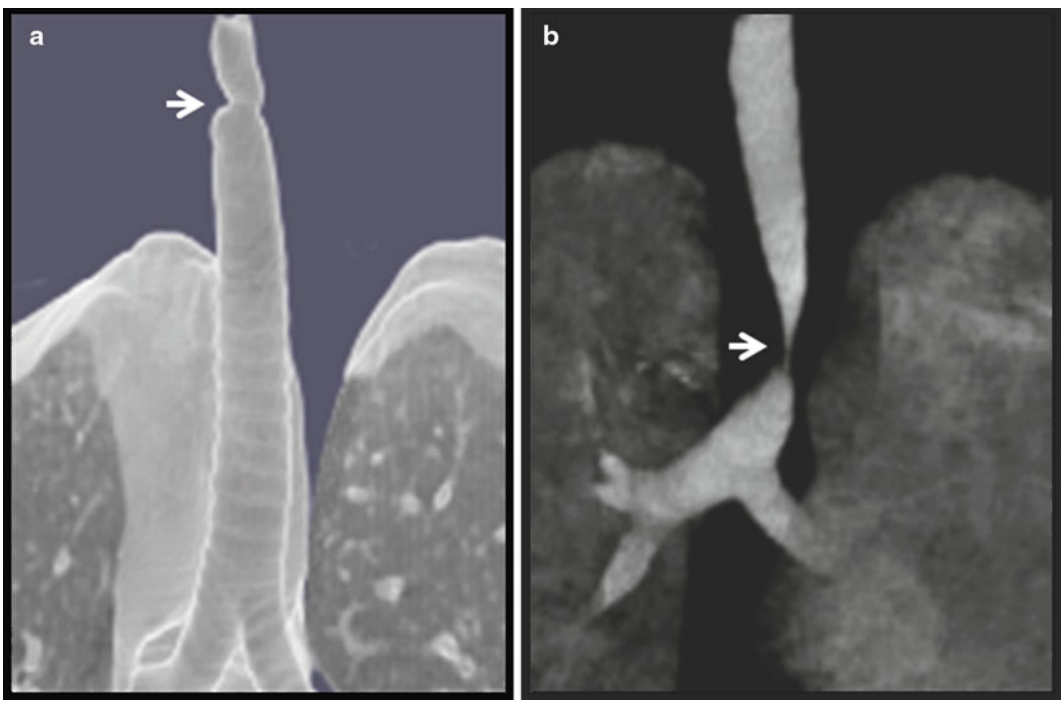

Fig. 26.9 Three-dimensional reconstruction computed tomography imaging showing (**a**) abrupt and (**b**) tapered transition zone

Newer modalities such as radial endobronchial ultrasound have not accumulated as much data in benign disease as compared to malignant airway obstruction in guiding therapeutic intervention. Nevertheless, endobronchial ultrasound can still be used to assess integrity of bronchial cartilages and identify malacia.

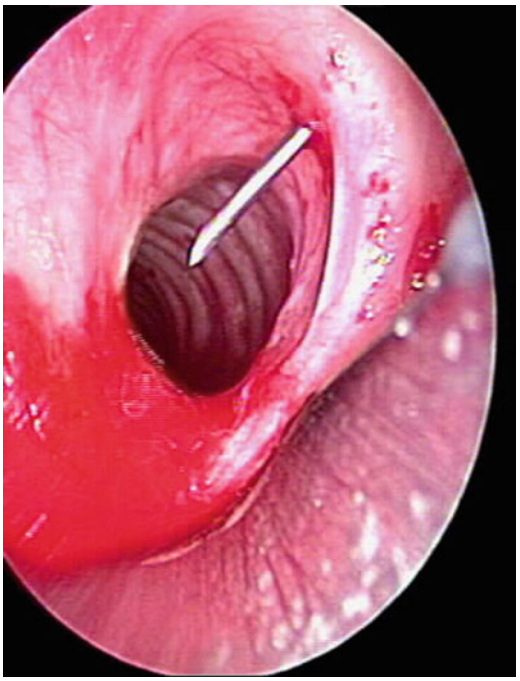

Fig. 26.10 Needle inserted through the cricothyroid membrane with the cricoid cartilage located immediately superior

Tracheobronchial Surgery

The surgical options for nonmalignant airway obstruction are resection with end-to-end anastomosis, sleeve resection, as well as tracheoplasty. Lesions that involve as much as half the trachea can be resected, and these procedures may include a laryngeal release. However, surgical correction of lesions ≥40 mm in length is more often associated with anastomotic complications such as granulation, stenosis, or dehiscence. Best results are achieved when surgery is carried out early because prior tracheotomy or stenting can extend a lesion. Preoperative optimization of a patient for surgery includes managing medical comorbidities, treating post-obstructive infections, weaning down systemic steroids, and allowing acute inflammation to settle. Patients on high-dose steroids are at particular risk of wound dehiscence. Postoperatively bronchoscopy may be also necessary to suction secretions, monitor anastomotic sites, and manage surgical complications.

Management by Pathology

Post-intubation/tracheotomy stenosis. This is the most common cause of benign tracheal stenosis in regions where the prevalence of tuberculosis is low. Post-intubation stenosis typically occurs at three locations: (1) medial surface of the arytenoids, (2) posterior interarytenoid space, and (3) subglottic space affecting the posterior laminar of the cricoid cartilage. Edema is followed by mucosal ulceration and then

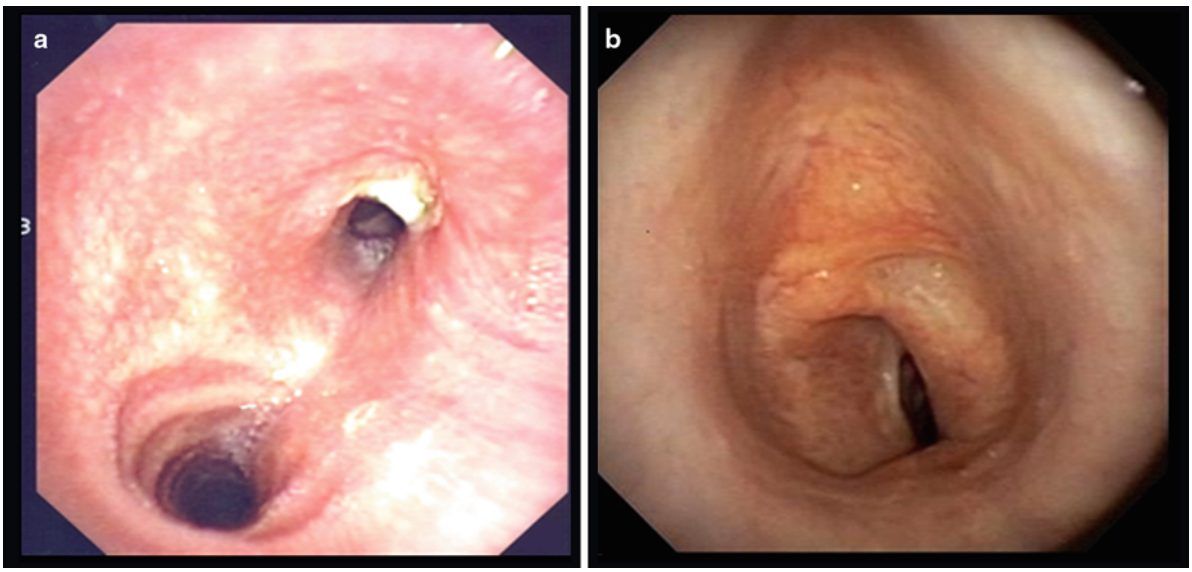

Fig. 26.11 (**a**) Edema, erythema, and exudates indicating inflammation in this patient with tuberculous endobronchitis and (**b**) pure fibrous lesion completely covered with normal mucosa in this case of post-tracheotomy stenosis

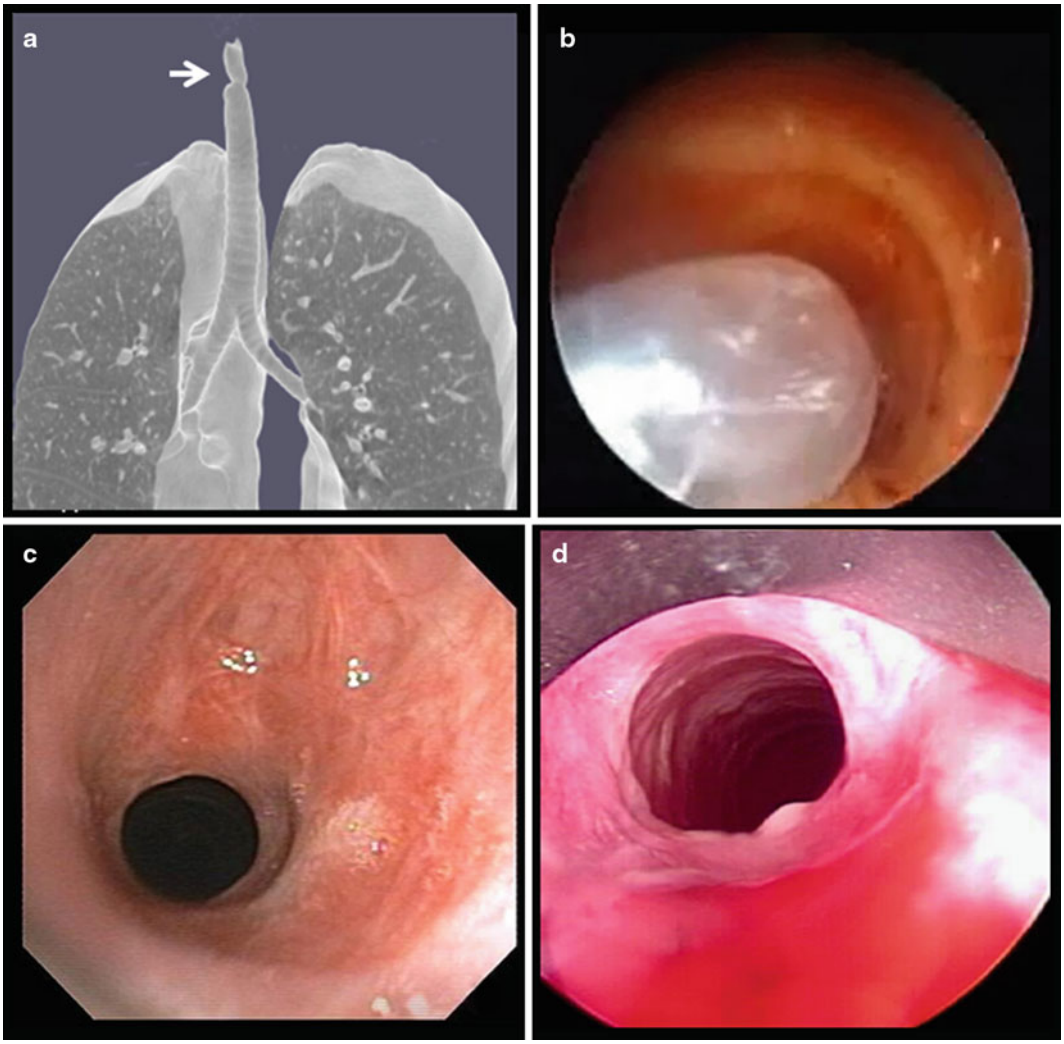

Fig. 26.12 Idiopathic subglottic stenosis treated with balloon dilation bronchoplasty, (**a**) three-dimensional reconstruction image, (**b**) balloon dilation, (**c**) pre-dilation, and (**d**) post-dilation bronchoscopic view

chondritis, before cartilage is damaged. There are also multiple sites at which tracheotomies can cause stenosis: (1) stoma, (2) inflatable cuff, (3) between the stoma and cuff, and (4) where the tracheostomy tip impinges the posterior tracheal wall. Stomal obstructions are either granulomas, posterior flaps above the stoma, or "A-shaped" stenosis due to cartilage fracture (Fig. 26.4). Cuff site lesions are ischemic pressure sores that start as tracheitis before maturing into circumferential stenoses. Lesions at other sites are granulomas, web-like stenosis, or complex lesions (Fig. 26.11). Complex lesions are >10 mm in length and hourglass shaped or have associated tracheomalacia.

Web-like stenosis can be treated endoscopically with laser resection and dilation, achieving success rates of 66–95%. A mucosal sparring technique should be used to preserve as much normal mucosa as possible. This involves making radial incisions with laser at the 3, 9, and 12 o'clock positions. Circumferential excision of lesions with removal of airway mucosa is avoided because the preserved mucosa is believed to assist in re-epithelization and healing.

Complex lesions may need to be stented after initial dilation. Dilation prior to stenting also enables the endoscopist to evaluate the full length of the stricture, the degree of mucosal inflammation, and the patency of the distal airway. There are two broad categories of dilation techniques. Rigid bronchoscopy barrels or semirigid bougie dilators of increasing sizes can be sequentially passed. Alternatively, saline or contrast-filled balloon dilation can be attempted (Fig. 26.12).

Patients should be considered for surgical resection if symptoms improve following a stent trial. Long-term stenting is only considered in nonsurgical candidates. Complex stenoses have high failure rates of >30% and often require more than three endoscopic attempts. Stents can augment dilatation or thermal ablation and serve as a bridge to

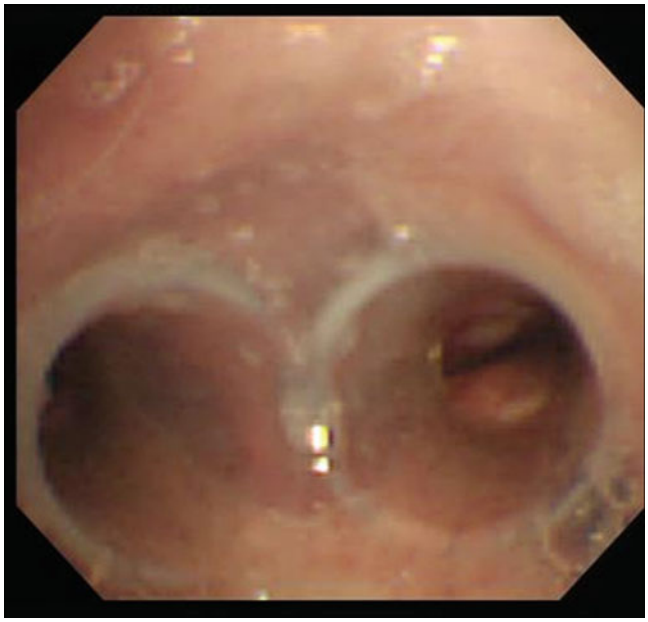

Fig. 26.13 Silicone Y-stent inserted in a patient with tracheomalacia

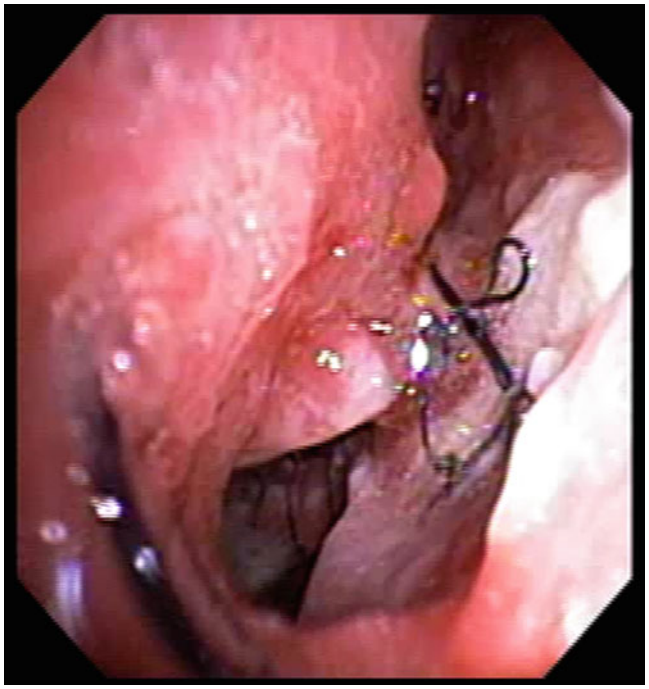

Fig. 26.14 Metal stent complications: fracture and granulation tissue

surgery by allowing inflammatory lesions to settle. Sometimes a stented stricture can mature and stiffen sufficiently such that after removal of the stent, the patients remain symptom free without the need for further intervention. Silicone stents are recommended for benign disease because they can be easily readjusted or removed following a stent trial (Fig. 26.13). Self-expanding metal stents are easy to insert, can be positioned without the need for rigid endoscopy, and have large internal to external diameter ratios. However, treatment success is usually short-term because of complications such as stent fracture (Fig. 26.14), occlusion with granulation tissue, and airway erosion. Furthermore, once deployed these stents require considerable expertise to remove. Anticipated complications of metal stent removal include retained stent fragments (28%), mucosal tears (16%), reocclusion requiring further stenting (56%), and tension pneumothorax (4%). This data prompted the United States Food and Drug Administration (FDA) to issue a public health notification on metal tracheal stents in patients with benign airway disorders in 2005. The recommendations state that metal tracheal stents should be used in patients with benign airway disorders only after thoroughly exploring all other treatment options such as surgery and silicone stents. The use of metal stents as a bridging therapy is also not advised.

Idiopathic Subglottic Stenosis

This condition typically affects women in their 30s and 40s with a background of gastroesophageal reflux. ANCA titers should be checked to exclude the possibility of Wegener's granulomatosis. Circumferential keloidal fibrosis and dilated mucous secreting glands are prominent without damage to the underlying cartilage. Spontaneous regression is not seen, and patients with simple, web lesions can have lasting results with laser incisions and dilations. Those with complex stenosis (Fig. 26.7) should be considered for surgical resection although this may not be possible for lesions extending to within 5 mm of the glottis.

Stenting is challenging because it is difficult to seat a tubular stent in the subglottic space and prevent migration. Instead, T-tubes are the prosthesis of choice if surgery is not an option and can be kept in situ for up to a year without changing. T-tubes should be sized such that the proximal limb does not impinge on the conus elasticus of the subglottic larynx and the distal limb traverses the entire stenosis. Excessively long distal T-tube limbs impede evacuation of secretions and irritate the mucosa into forming granulation tissue. Patients should be thoroughly evaluated and treated for gastroesophageal reflux to avoid recurrence. Mitomycin C has also been used to prevent recurrence. This is a naturally

occurring antibiotic isolated from *Streptomyces caespitosus* and in low concentrations inhibits subepithelial fibroblast proliferation. Pledgets soaked in 0.4 mg/ml of mitomycin C are applied to lesions for 1–2 min.

Systemic Inflammatory Disorders

Airway complications of Wegener's granulomatosis include subglottic stenosis, as well as circumferential or ulcerative bronchial stenosis. The varied presentation, good response to systemic immunosuppression, and impaired postoperative healing due to poor vascular supply favor a nonsurgical approach. Laryngotracheoplasty is therefore deferred because of the high risk of restenosis, and initially, a combination of endoscopic and systemic therapy is pursued. Intralesional steroids with 40–120 mg of methylprednisolone injected into the submucosa of scar tissue before either laser or dilation therapy have also had success in prevention of recurrence.

Relapsing polychondritis is characterized by inflammatory degeneration of cartilage, and the prevalence of airway involvement is about 20%. Initial obstruction is caused by edema before cartilage damage results in malacia. Immunosuppression with steroids, mycophenolate, etanercept, or methotrexate is the mainstay of treatment. Although surgical or endoscopic interventions are limited when the pathology is diffuse, high tracheal lesions may necessitate a tracheotomy. Palliation of focal lesions can be achieved by balloon dilation and/or stenting.

Airway stenosis is a rare manifestation of sarcoidosis and is caused by either granulomatous infiltration of the bronchial wall or extrinsic compression by enlarged lymph nodes. The right middle lobe is most commonly affected due to its small orifice, sharp angulation from the bronchus intermedius, and large number of surrounding hilar lymph nodes. The three main patterns of involvement are single, multiple, or diffuse airway narrowing with multiple stenoses as the most frequent presentation. These lesions are often refractory to systemic steroids or even second-line immunosuppressive agents such as hydroxychloroquine or methotrexate. Surgical options are not used because of the relapsing or sometimes progressive nature of the disease. Temporary palliation of localized stenosis can be achieved with balloon dilation and augmented immunosuppression, while stenting is reserved for cases with associated tracheobronchomalacia.

Tuberculous Stenosis

This pathology is predominantly reported in females of East Asian origin and is frequently sited in the left main stem bronchus. Active tracheitis (Fig. 26.11) can be ulcerative or polypoid, while chronic lesions are fibrotic, malacic, or both. Balloon dilation is preferred in the acute phase but is usually unsuccessful in chronic lesions because of submucosal fibrosis and remodeling. Excessive dilation may even damage the underlying cartilage without any improvement in the patency of rigid strictures. The presence of long segments (>10 mm), bronchomalacia, and previous failure of repeated (>3) balloon dilations are indications for stenting. However, active tuberculosis can spread along a stented trachea despite the concurrent use of appropriate antimicrobials, and endoscopy should be deferred till treatment is complete. Stents are replaced annually as the stricture matures and can be eventually removed in over 70%. Of these patients, 90% will maintain long-term airway patency. If endoscopic interventions fail, a surgical sleeve resection may be necessary because most lesions are too long for end-to-end anastomosis after resection.

Fungal Infections/Broncholiths

Histoplasmosis can cause airway obstruction by direct compression from enlarged calcified lymph nodes or by erosion of lymph nodes into airways causing broncholiths. Broncholiths either obstruct the airway lumen or cause hemoptysis by triggering the development of granulation tissue and most commonly affect the bronchus intermedius. Caution must be exercised in the endoscopic removal of broncholiths because the endobronchial component may represent the "tip of the iceberg" of a much larger lesion that would require a thoracotomy with broncholithectomy. Despite surgery, recurrence or persistence of stenosis can occur in nearly 15% of cases.

Papillomatosis

Laryngotracheal papillomatosis is associated with the human papilloma virus. Children present with more severe airway obstruction than adults, and lesions can occur either at the vocal cords or in the airways. These protuberant intraluminal lesions (Fig. 26.4) can be managed by microdebrider debulking or "painting" with laser coagulation and subsequent forceps debulking. A microdebrider is composed of a hollow metal tube with a rotating blade (1,000–3,000 rpm) that is coupled to suction. This allows obstructing tissue to be dissected while simultaneously evacuating debris and blood. Sessile lesions can be just coated with laser and allowed to slough off. There is also emerging data on the successful use of pulsed-dye laser targeting microvasculature, intralesional interferon α, oral indole-3-carbinol, intralesional cidofovir, and photodynamic therapy with dihematoporphyrin ether (DHE).

Other Infections

Nocardiosis typically affects immunocompromised individuals and can cause hemoptysis by erosion through the airway walls into blood vessels. Patients with a history of Diphtheria can present many years later with either tracheal or subglottic stenosis. However, this stenosis may be attributable to previous intubation rather than the diphtheria infection. *Klebsiella rhinoscleromatis* typically causes chronic inflammation and sclerosis in the nasopharynx and larynx. Subglottic webs have also been reported and may be again associated with prior intubation. For all these lesions, active infection should be first treated with antimicrobials and the surgical option of resection with anastomosis considered before offering endoscopic therapy. HIV also has a wide range of airway pathology as Kaposi's sarcoma, bacterial/tuberculous tracheitis, non-Hodgkin's lymphoma, and aspergillosis. These are all treated with either radiotherapy or antimicrobials.

Extrinsic Compression/Distortion of Airways

The pathology is often dual: (1) initial narrowing by direct compression and (2) subsequent malacia from cartilage damage. Although surgical resection of the cause of obstruction is recommended for thyroid goiters and mediastinal cysts, the trachea may collapse following the removal of the adjacent lesion. Such potential for malacia must be indentified preoperatively and managed with either stenting or tracheal reconstruction. Vascular slings (Fig. 26.3) and post pneumonectomy syndromes which distort the trachea are ideally managed surgically by attempting to restore the normal anatomical relationships of the mediastinum. Stenting is relatively contraindicated in patients with vascular compression because of the risk of stent erosion and fatal fistulation.

Amyloidosis

Endobronchial disease is more often associated with localized rather than systemic amyloidosis and is characterized by either submucosal plaques or polypoid airway tumors. Definitive therapy is with moderate dose (20–24 Gy) external beam radiation that can destroy plasma cells which secrete amyloid proteins. Repeated debulking with forceps is commonly required with the anticipated complication of bleeding. Successful stenting and laser resection have also been reported. Tracheotomy may be needed to bypasses subglottic disease that is not amenable to endoscopic treatment. Colchicine is thought to retard the synthesis, deposition, and degradation of amyloid in tissues and can be used as adjunctive therapy.

Tracheopathia Osteoplastica

In this rare, progressive disorder, there are multiple osseocartilaginous nodules that are distributed over the cartilaginous surfaces of the tracheobronchial tree with sparing of the posterior membranous wall. These submucosal lesions are rock hard making it difficult to biopsy or dilate. No single treatment option has been found to be universally successful, and endoscopic debulking, cryotherapy, and laser excision, as well as external beam radiotherapy, have been attempted. Holmium laser has both cutting/coagulating properties and is particularly useful in ablating the osseous nodules. Surgical correction can be attempted by linear tracheoplasty and subsequent stenting with a silicone T or T-Y tube until healing is complete.

Hemangioma

Subglottic hemangiomas are congenital vascular malformations that present in the first year of life. These sessile and compressible lesions are located on the posterolateral airway surface. Asymptomatic lesions are managed by only observation until complete regression occurs. If there is airway obstruction, laser ablation is successful, but treatment should be undertaken in a staged manner to avoid subsequent subglottic stenosis. Surgical excision can be challenging because these lesions are neither discrete nor surrounded by a capsule.

Dynamic Airway Compression

Paired end-inspiratory and expiratory CT, as well as dynamic imaging, has revolutionized the diagnosis of these disorders with excellent correlation to bronchoscopic findings. The noninvasive treatment option is continuous positive airway pressure (CPAP) that serves as a pneumatic splint.

The management challenge of tracheomalacia is identifying the exact flow-limiting segments. The severity of expiratory flow limitation at rest is often not related to the degree of tracheal collapsibility because flow limitation can concomitantly occur in the peripheral airways. In some cases, stenting also causes distal migration of the choke points. Therefore, short 2-week stent trials should be used to assess the correct site of intervention and to evaluate the success of treatment. Patients with such a successful stent trial are then considered for surgical repair because of the high complication rates associated with prolonged stenting. The surgical option for focal tracheomalacia is resection with end-to-end anastomosis, while diffuse disease is treated with tracheoplasty. Tracheoplasty involves stabilization of the posterior tracheobronchial membrane with a polypropylene mesh and has

been shown to improve quality of life, as well as functional status. Tracheomalacia is also seen in patients with tracheobronchomegaly, i.e., Mounier-Kuhn syndrome, and these patients can be managed with customized, large Y-stents.

Conclusion

Successful management of benign airway stenosis involves immediate stabilization, careful assessment, meticulous planning, and individually tailored treatment. Each lesion requires an approach that is based on the understanding of pathophysiology and natural history of disease. Despite the availability of a wide range of endoscopic options, patients should not be denied surgery too lightly. Endoscopy, although effective in evaluation, stabilization, and palliation, seldom provides curative outcomes. Repeated therapeutic bronchoscopy exposes physiologically fragile patients to repeated risks and anesthesia. Inappropriate endoscopic treatment can also worsen tracheal damage through iatrogenic complications. Therefore, long-term treatment via endoscopy in nonmalignant airway obstruction should only be attempted when surgical options are unavailable or undesired. Lesions >10 mm in length, with associated malacia and the presence of circumferential scarring or cicatricial contracture, predict failure of endoscopic techniques.

Empowering patients to make informed decisions with appropriate explanations on the relative benefits and risks of each option is an under-emphasized component of decision-making. Patient education encourages realistic expectations of treatment results and enables early troubleshooting of complications. Effective communication also extends to colleagues because the current state-of-the-art treatment involves a multidisciplinary team involving pulmonologists, thoracic surgeons, anesthetists, otolaryngologists, and radiologists. What intervention a particular patient receives and who provides it depend on the site, severity, extent, underlying pathology, and presence of complicating factors. These factors include laryngeal involvement, tracheobronchomalacia, airway inflammation, and post-obstructive infection. Furthermore, the choice of treatment is influenced by the stability of the patient, availability of local expertise/technology, and intent of treatment, i.e., palliative or curative. The culmination of all these factors dictates how we utilize the surgical and endoscopic options available to us in the management of nonmalignant airway obstruction.

Acknowledgments Adnan Majid from Interventional Pulmonology, Beth Israel Deaconess Medical Center, and Low Su Ying from Respiratory and Critical Care Medicine, Singapore General Hospital, contributed bronchoscopy images.

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Rigid Bronchoscopy

27

Jed A. Gorden

Introduction/Indications

This chapter will focus on the art of rigid bronchoscopy, its versatility, and many applications. While more technology and instruments are being adapted to the flexible bronchoscope, this does not render the skill set associated with rigid bronchoscopy obsolete. The rigid bronchoscope remains the therapeutic instrument of choice for the airway. The large caliber and stiff construction of the rigid bronchoscope allows the endoscopist to access and manipulate the entire trachea as well as the right and left proximal airways. With the rigid bronchoscope in place, the airway is no longer a simple source for oxygenation and ventilation or a passive conduit to the respiratory tract like a traditional endotracheal tube but a powerful direct therapeutic tool. Bronchoscopy serves two main purposes: diagnostic data collection and therapeutic intervention. Since the introduction of the flexible bronchoscope, the primary role of the rigid bronchoscope has been in the therapeutic management of airway pathology. The principle indications for rigid bronchoscopy include large tissue biopsies, removal of complex foreign bodies, management of massive hemoptysis, and therapeutic interventions for intrinsic airway obstruction and extrinsic airway compression secondary to malignant and benign pathology (Table 27.1).

The lung cancer epidemic of the mid-twentieth century has made rigid bronchoscopy a vital skill when managing patients with advanced lung cancer. It is estimated that up to 20–40% of patients who suffer from lung cancer will experience an episode of mechanical airway obstruction. In cases of symptomatic airway compromise, the intervention should be rapid and effective with low associated morbidity and mortality. If performed as a staged procedure to establish a stable airway prior to more definitive surgical management, the endoscopic intervention should not interfere with the ultimate surgical plan. If the intervention is palliative, it should require limited follow-up care in an effort to maximize the positive impact on patient quality of life.

The rigid bronchoscope alone is an effective tool and satisfies the above goals.

There are numerous specific technical advantages to the rigid bronchoscope in comparison to the flexible bronchoscope that need to be emphasized, including large volume suction capability, direct airway control, greater therapeutic options, and stent placement (Table 27.2). It is important to remember that the flexible bronchoscope complements the rigid bronchoscope and should not replace it in the airway armamentarium.

In order to provide multidimensional patient care, the therapeutic endoscopist of the twenty-first century needs to be facile in both the technology first conceived in the nineteenth century and that which was introduced in the twentieth century.

Equipment

The rigid bronchoscope is a powerful yet simple piece of equipment. The rigid bronchoscope acts as a conduit to the airway and accommodates a variety of tools: graspers, dilators, biopsy forceps, stent delivery devices, catheters, and suction devices. There are three main components of the rigid bronchoscope: the barrel, the multifunction head, and the optics and light source.

1. *The Barrel*: There are two main varieties of rigid scopes: rigid bronchoscopes and rigid trachea scopes. Rigid bronchoscopes are longer permitting access to the right and left bronchial tree and have side ventilation fenestrations. The rigid trachea scope is shorter, has no side ventilation fenestrations, and cannot reach past the mid- to distal trachea (Fig. 27.1).

   The rigid barrel is a hollow metallic tube with a beveled distal tip. The proximal end of the scope connects to the multifunction head permitting ventilation and instrument

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access. The light source attaches to the proximal end of the scope or to the telescope lens directly depending on the make and model. Rigid bronchoscopes are manufactured in various lengths ranging from 33 to 43 cm depending on type and manufacturer. Rigid scopes have both an inner and an outer diameter. The inner diameter of the adult rigid bronchoscope ranges from approximately 7–13 mm, and the outer diameter ranges from 8 to 14 mm depending on the specific scope and manufacturer. Scope size is a critical component of clinical decision making in therapeutic bronchoscopy. Larger scopes can accommodate large stents including Y stents and are excellent for addressing tracheal and proximal mainstem pathology. Smaller scopes can more easily navigate the distal left and right mainstem bronchi, and the bronchus intermedius but may be more limiting as a conduit for certain larger instruments and stents. Smaller scopes can be used serially to access and dilate tight stenosis, minimizing the risk of airway trauma caused by larger scope diameters.

2. *The Multifunction Head*: The multifunction head attaches to the proximal portion of the barrel. The multifunction head (Fig. 27.2) has ports to accommodate ventilation and procedural instruments or suction simultaneously. The ventilation port can be attached to either volume ventilation or jet ventilation depending on one's preference. The rigid bronchoscope is uncuffed, therefore a significant air leak may occur and the tidal volumes delivered will not reflect alveolar tidal volume. Furthermore, it may be difficult to assess end tidal CO2. Jet ventilation allows the operator to maintain an open circuit and freely introduce and remove instruments. Volume ventilation requires a fenestrated cap which must remain closed to ensure adequate ventilation.
3. *Optics and Light Source:* For intubation, the endoscopist can either use a telescope and camera to direct the rigid scope or direct visualization down the barrel with the naked eye using the light source built into the barrel

Table 27.1 Indications for rigid bronchoscopy

Large volume tissue biopsies
Management of massive hemoptysis
Foreign body extraction
Direct management of endobronchial obstruction
Mechanical coring of lesion using beveled tip
Direct dilation of airway lumen
Indirect management of endobronchial obstruction
Nd:YAG laser
Argon plasma coagulation (APC)
Cryotherapy
Electrocautery
Bougie/balloon dilation
Microdebrider
Management of extrinsic/dynamic airway lumen compression
Silicone stent
Self-expandable stent

Table 27.2 Advantages of the rigid bronchoscope

Large lumen accommodates variety of larger tools and devices
Large suction capability
Ventilating lumen minimizes airway obstruction
Ability to deploy silicone and expandable stents
Direct ability to manipulate lesions and achieve hemostasis
Decreased risk of airway fire when using heat energy
Direct airway control
Direct ability to isolate right and left airway
Well-supported oxygenation and ventilation throughout procedure
Allows for prolonged procedures

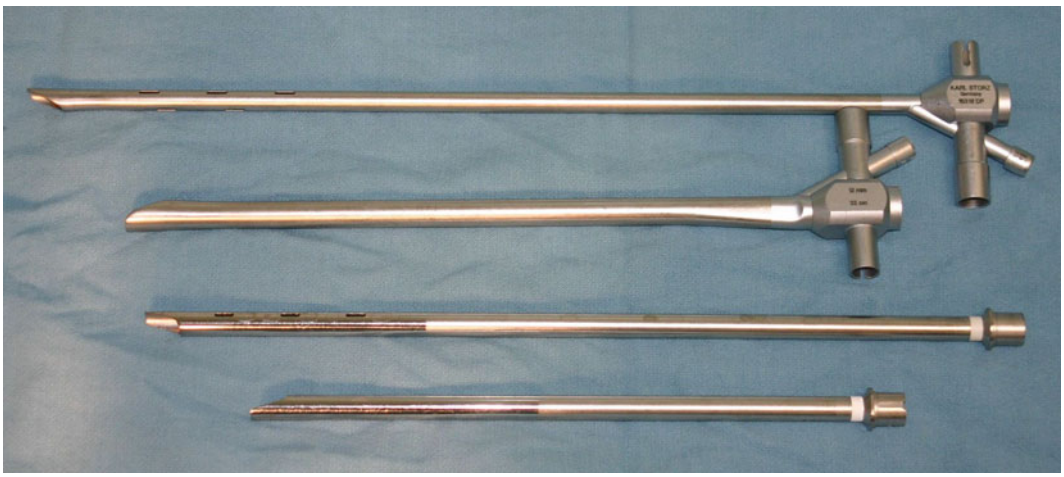


Fig. 27.1 Rigid bronchoscope and rigid tracheascope. The rigid bronchoscope is long and has side ventilating fenestrations at its distal end. The rigid trachea scope is shorter and has no side ventilating fenestrations

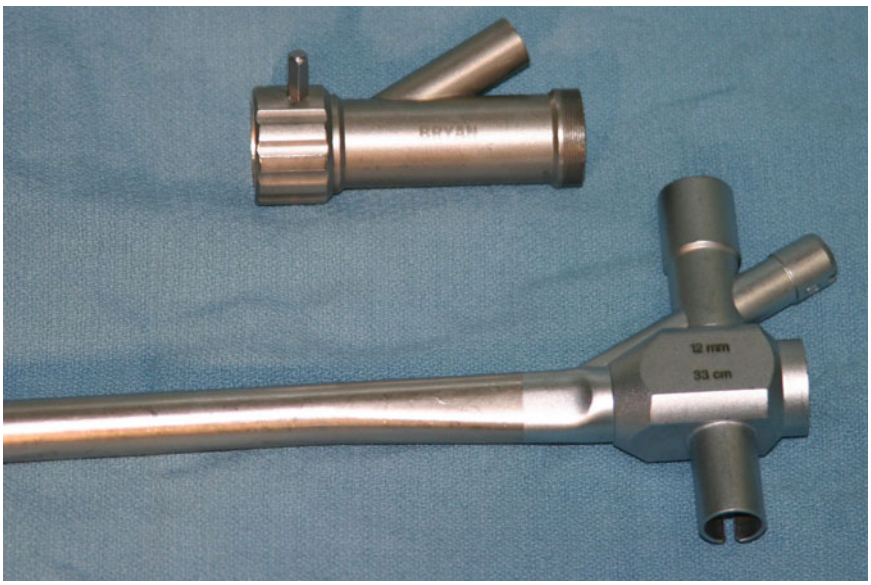
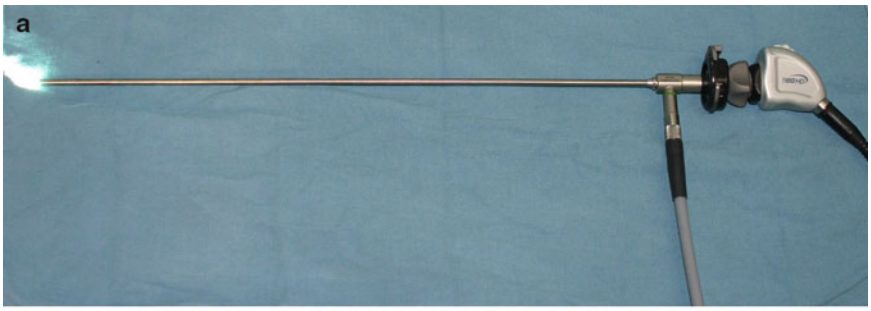


Fig. 27.2 The multifunction head can be an independent piece which attaches to the rigid barrel or is a unified extension of the rigid barrel. The multifunction head allows for simultaneous ventilation and airway instrumentation



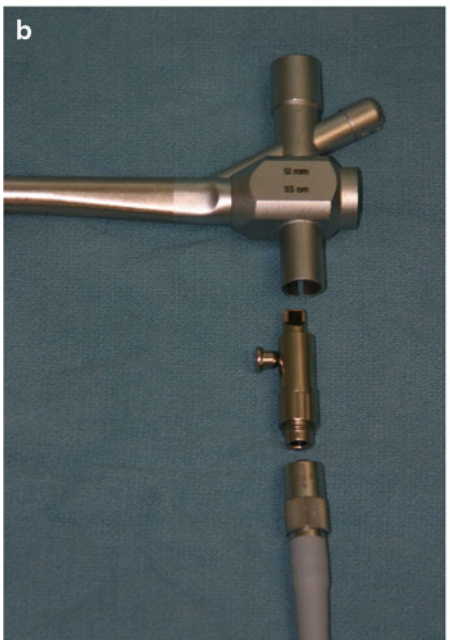


Fig. 27.3 (**a**) The bronchoscope light source can be attached to a video telescope displaying the image on a monitor. (**b**) The light source can be built into the multifunction head allowing the bronchoscopist to directly site down the barrel into the airway

(Fig. 27.3). Once the airway is secured, the bronchoscopist can deploy a telescope coupled to a camera, pass a flexible bronchoscope, or employ optical forceps which combine the telescopic camera and specialized graspers for visualization. Some endoscopists site directly down the barrel with the naked eye for instrument deployment. Only bronchoscopes with a built-in light source allow the endoscopist direct sight through the lumen of the scope.

Our practice routinely employs both rigid and flexible bronchoscopy concurrently for all procedures. The flexible

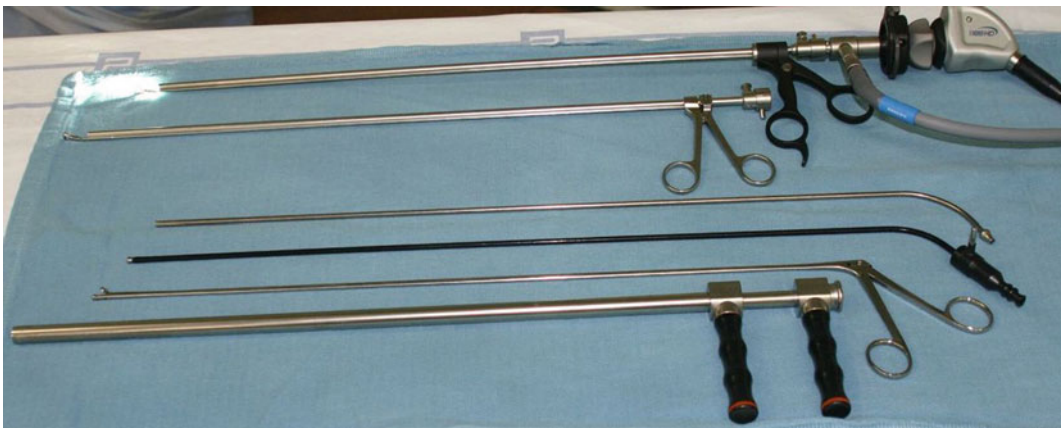


Fig. 27.4 Rigid bronchoscope accessories for deployment down the barrel

bronchoscope can also be inserted to extend the endoscopy into the lobar and segmental levels, to inspect the airway beyond obstructing lesions or areas of bronchial distortion.

Tools and Accessories: Instruments have been designed to pass through the main working lumen or barrel of the bronchoscope. Principle accessories include suction catheters, graspers, biopsy forceps, dilators, cautery, stents, and other implements (Fig. 27.4). The common feature of instruments designed for the rigid bronchoscope is that they are larger and stiffer than those built for the working channel of the flexible bronchoscope.

Technique

Intubating the patient with the rigid bronchoscope requires appropriate sedation and proper patient positioning. Sedation and use of paralytics depends on the clinical stability of the patient, presence or absence of central mediastinal tumors, and careful communication between endoscopist and anesthesiologist.

The scopes' rigid construction requires straight and direct access to the larynx. As with all intubations, the teeth are vulnerable, and a tooth guard should be placed to protect the upper teeth during the procedure. When proper technique is employed, there should be no pressure on the upper teeth or lip similar to direct laryngoscope intubation. The patient is positioned supine with either a towel roll under the shoulders or the head of the bed dropped allowing the neck to be maximally extended without floating. This maneuver elevates the larynx and creates a more linear route through the vocal cords. The goal is to achieve anterior linear alignment of the oral, pharyngeal, and laryngeal axis in order to access the trachea (Fig. 27.5).

Once the patient is positioned, the bronchoscope is used to directly intubate the trachea and advanced under direct visualization either sighting directly down the barrel or through the telescope and camera optics. It is critical to advance the scope under direct visualization to ensure midline position. If employing the telescope and camera technique, the telescope should always remain within the barrel

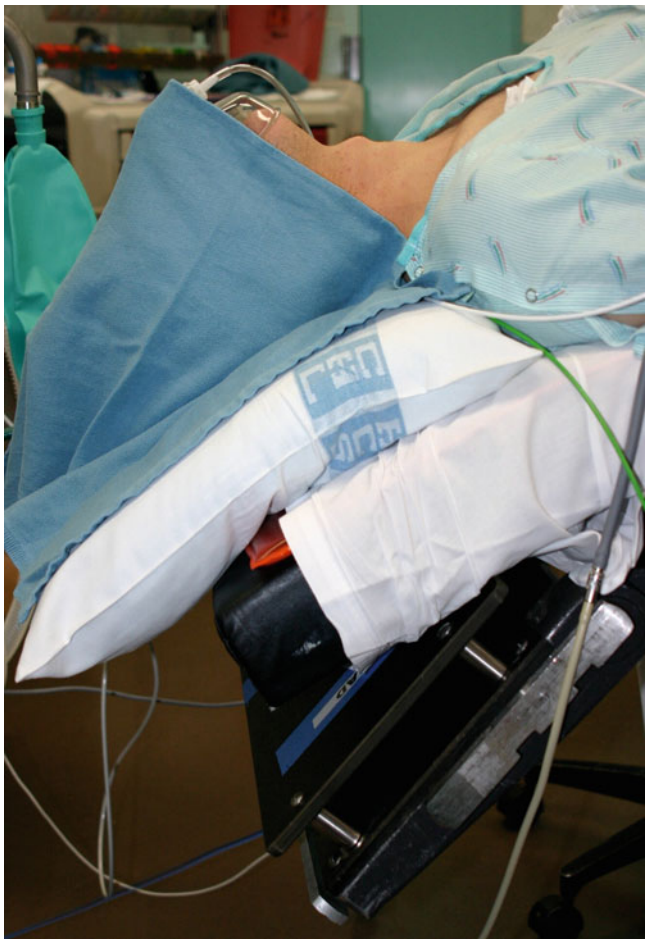


Fig. 27.5 Patient position in preparation for rigid bronchoscopy intubation

of the scope with visualization of the distal scope tip at all times to minimize risk of airway injury (Fig. 27.6). The endoscopist uses their nondominant hand and the first finger to push the jaw down. The second finger rests on the roof of the patient's mouth, and the thumb acts as a fulcrum supporting the scope. The scope, held in the dominant hand, is inserted into the oral cavity perpendicular (at a 90 ° angle) to the operating table. The first visualized structure is the uvula as the scope is advanced to the base of the tongue (Fig. 27.7). When the uvula comes into view, the hand supporting the scope drops using the thumb as a fulcrum, from a 90 ° angle to an approximately 45 ° angle. The scope is now advanced until the epiglottis comes into view (Fig. 27.8). Care is necessary to keep the scope pressure on the operators thumb near the mouth, rather than on the patient's teeth. The scope is passed under the epiglottis, which is lifted directly anterior to expose the larynx and vocal cords. With the vocal cords visualized and open, the scope is rotated 90 ° to the right or left, so the bevel is parallel to the cords to minimize vocal cord trauma (Fig. 27.9). Once past the cords, the scope is advanced to the mid-trachea to ensure the distal lateral ventilation ports are well within the airway and the ventilating system can be attached to establish active ventilation.

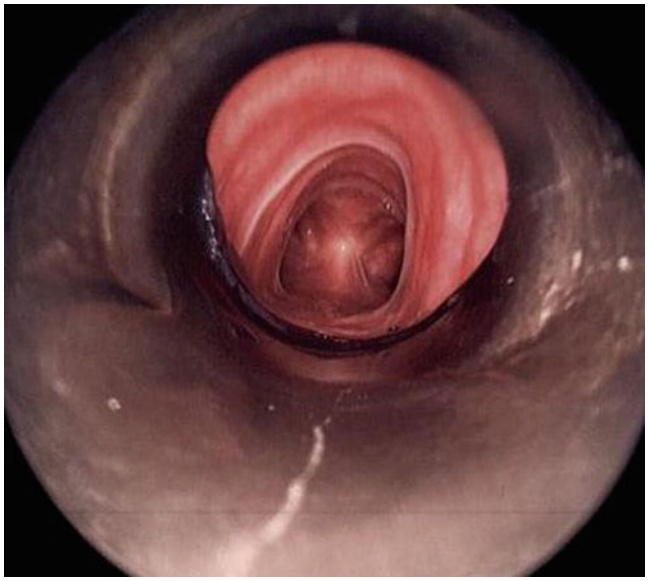


Fig. 27.6 View of the light source and telescope safely tucked in the rigid barrel. This is the view you should have of the distal tip when advancing the rigid bronchoscope

Given the inflexibility of the rigid bronchoscope, it can only be advanced in a linear path and cannot access subsegmental airways. The airways most accessible to the rigid bronchoscope include the right mainstem bronchus, bronchus intermedius, and the left mainstem bronchus. To enter the right mainstem bronchus, the patient's head is turned toward the left, creating a straight path to the right mainstem bronchus. To access the left mainstem bronchus, the patient's head is turned toward the right. The movement of the head helps create a straight path to the desired airway. Clear visualization of the distal end of the scope with simultaneous

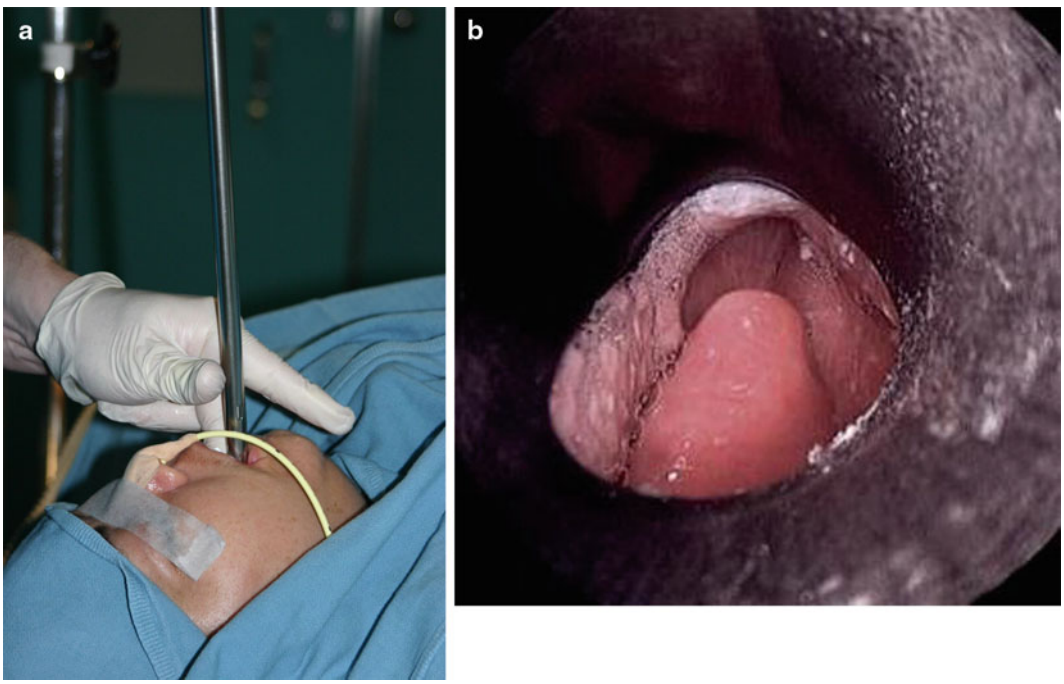


Fig. 27.7 (**a**) Initial position for rigid intubation. The scope is held perpendicular to the patient's oral pharynx. (**b**) In this position, the first structure you should visualize is the uvula

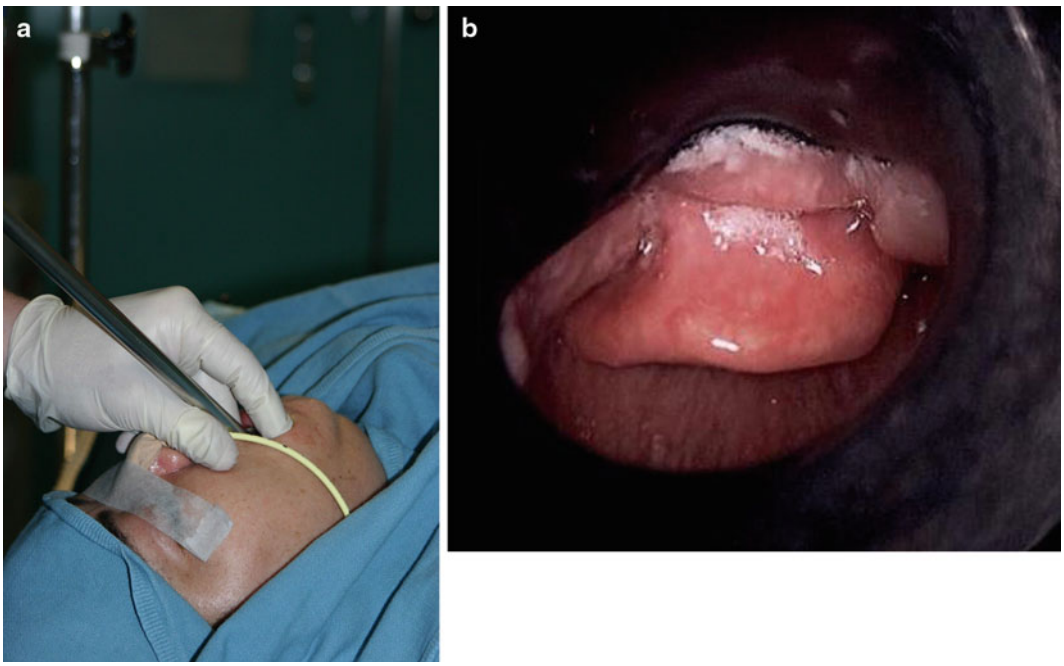


Fig. 27.8 (**a**) The second position for rigid intubation. The scope drops to a 45 ° angle. (**b**) In this position you should visualize the epiglottis

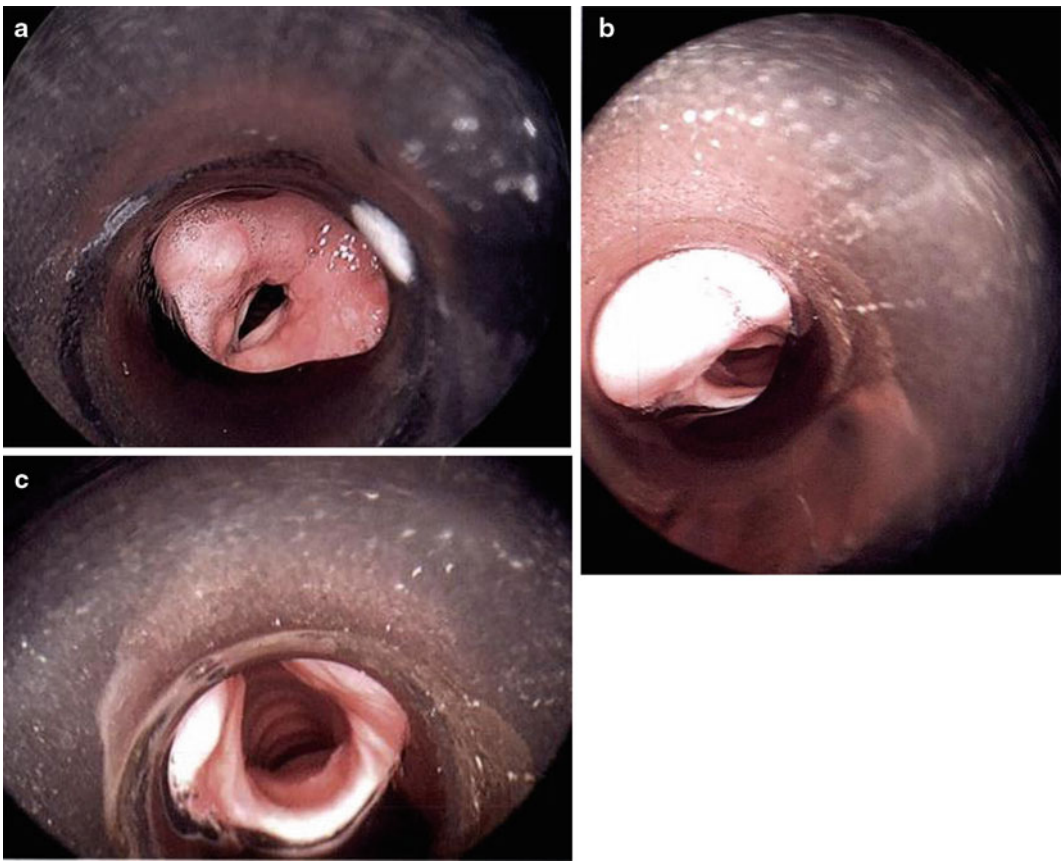


Fig. 27.9 Intubation of the vocal cords. (**a**) Rigid bevel at 12 o'clock initial visualization of the cords. (**b**) Rigid bevel is turned clockwise to 3 o'clock to separate the cords. (**c**) Rigid barrel is turned clockwise to 6 o'clock to pass the cords

view of the airway lumen is essential when manipulating the scope. Loss of orientation can risk serious injury to the airway, even airway perforation.

Operating Theater/Endoscopy Center

Rigid bronchoscopy requires an advanced care setting with qualified staff.

The team needs to include an anesthesiologist or certified nurse anesthetist to control patient safety and sedation, freeing the endoscopist to concentrate on procedure performance. The procedure and patient population are not appropriate for conscious sedation and minimally monitored settings. The bronchoscopist must be present before anesthesia is initiated to help ensure an adequate secure airway is obtained. Timing and coordination with anesthesia is critical when managing patients with complex airway pathology. When rigid bronchoscopy is performed, the bronchoscopist intubates and controls the airway necessitating proper communication between the endoscopist and anesthesia. Because rigid bronchoscopy involves an open circuit, volatile gasses are avoided, and intravenous anesthesia is used.

Additional members of the team include a trained bronchoscopy assistant familiar with all the equipment required for the procedure. The patient should be appropriately monitored with IV access, pulse oximetry, blood pressure, and heart rate monitoring. End tidal CO_2 monitoring is unreliable due to the lack of a closed circuit, and teams may use an arterial line to monitor ventilation, though it is not required. The unit and team must be able to handle both the complexity of an often critically ill patient and a complex procedure.

Therapeutic Bronchoscopy

The rigid bronchoscope is best suited for complex therapeutic airway procedures, most of which will be discussed in depth elsewhere in this reference text. Here, we will highlight some of the key procedures suited to rigid bronchoscopy and emphasize the superiority of the rigid bronchoscope in airway management.

Tumor Excision

Central airway obstruction (trachea, carina, mainstem bronchi, and bronchus intermedius) causing internal luminal obstruction (intrinsic obstruction) (Fig. 27.10) requires tools to achieve tumor excision. Debulking an intraluminal tumor requires a stable and secure airway, rapid access to varied large instruments, and immediate access to large-bore suction and tools for hemostasis. All this can be achieved using the rigid bronchoscope.

Endobronchial lesions can be effectively removed either with biopsy forceps or the cryoprobe (mechanical debridement), using the beveled tip of the bronchoscope directly (coring out) or by using the mechanical microdebrider to morselize and aspirate the offending lesion. When evaluating the obstructed airway, all secretions and blood should be suctioned in order to adequately visualize the obstructing

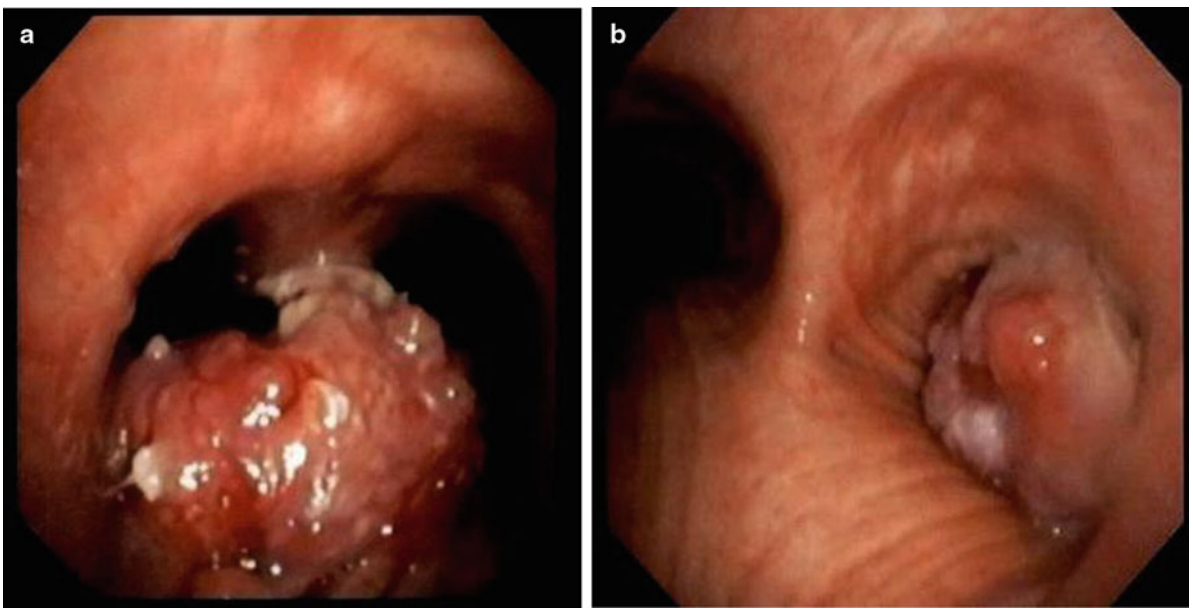


Fig. 27.10 Intrinsic airway obstruction. (**a**) Tracheal tumor obstructing left mainstem bronchus. (**b**) Right upper lobe tumor obstructing the right mainstem bronchus

lesion and ascertain the origin and extent of obstruction. It is critical to determine the axis of the airway and maintain this spatial orientation during the entire procedure. The obstructing lesion should be instrumented in parallel to the axis of the airway to avoid perforating the airway or breaching a vascular structure. In cases of intrinsic airway obstruction, the endolumenal tumor has often invaded the airway wall, and normal mucosal planes no longer exist. It is thus critical to maintain the proper spatial orientation and a clear view of the working field unobscured by blood or mucous.

The rigid bronchoscope alone can be used directly as a tool to relieve airway obstruction. To remove the obstructing lesion by coring out with the rigid bronchoscope, place the beveled tip of the bronchoscope against the base of the lesion and with a gentle twisting motion, with forward pressure, bluntly dissect the lesion off the airway wall under direct visualization. It is critical to inspect airways distally as well as the contralateral airway to ensure it remains free of debris, blood, or mucous. In our experience and published case series, rigid bronchoscopic blunt dissection of obstructing tumors rarely results in severe bleeding. The rigid bronchoscope is well suited to directly achieve hemostasis in the proximal airway. Minor bleeding can be addressed by direct tamponade with the rigid bronchoscope, directly pressing the barrel of the scope against the mucosal surface. While the risk of severe bleeding is very low, the operator must be cautious when approaching highly vascular tumors. In our experience, vascular tumors like carcinoids and renal cell carcinoma metastases are not contraindications to this method but must be approached with caution and preparation with large-bore suctioning and a clear plan for achieving hemostasis.

Large instruments like the microdebrider require the generous lumen of the barrel of the rigid bronchoscope to access the airway. The microdebrider is a morselizing and aspirating tool borrowed from our ENT and orthopedic colleagues and was adapted to the airway in 2005. The microdebrider is a hollow metal tube deployed under direct telescopic visualization with an internal rotary blade. The blade has a hockey stick shape and can be rotated 360 °. Under direct visualization, the device uses suction and direct contact to entrain tissue into the internally housed blades, and blood and tissue are removed from the field by suction maintaining an unobscured working field.

Tumor Destruction

When managing central airway pathology, it is critical to maintain hemostasis. Many tumors when manipulated will develop a raw surface and bleed. Small volumes of blood in the airway can result in significant oxygenation problems. Therefore, a plan for hemostasis when managing intrinsic airway obstruction is essential. Simple hemostasis can be achieved using topical iced saline or topical dilute epinephrine. The rigid bronchoscope is uniquely positioned to support more complex airway and tumor bleeding by facilitating large volume suction as well as support a diverse array of tools for hemostasis. The optics can also be withdrawn to visualize tools operating at the bleeding surface. Flexible bronchoscopy does not permit this offset of optic and tool as the video chip is at the same level as the suction port soiling the optics every time suction is applied to a bleeding surface.

The first and most direct tool for hemostasis is direct tamponade of the bleeding surface using the barrel of the rigid bronchoscope. The rigidity of the scope barrel is uniquely capable of being directed to the bleeding source and applying pressure.

Alternative tools for hemostasis include electrocautery and argon plasma coagulation (APC). Cautery uses electrical current to achieve thermal tissue destruction. Borrowing from the mediastinoscopy arena, the insulated cautery wand is uniquely suited to work in the airway. The cautery wand has an insulated shaft and active cautery tip with built-in suction channel allowing combined suction to clear the visual field and cautery to achieve hemostasis. The rigid cautery wand is deployed down the barrel of the bronchoscope under direct visualization with the telescope. Argon plasma coagulation uses ionized argon gas charged with an electrical current to achieve thermal tissue destruction. Unlike cautery APC does not require direct tissue contact with the probe. Tissue destruction occurs up to depths of 3–4 mm. Argon is delivered through a soft flexible catheter and therefore must be deployed through the working channel of the flexible bronchoscope in order to direct its delivery. The rigid bronchoscope is used to isolate the tumor, and then the flexible scope is used to direct the desiccating energized argon gas.

It is critical to remember when deploying heat energy of any kind in the airway that a low oxygen environment is required to minimize the risk of airway fire. Clear communication and coordination with anesthesia when using heat energy to decrease the delivered oxygen level and allow for an appropriate washout time will ensure patient safety.

Stent Placement

Central airway obstruction can also come in the form of extrinsic compression (Fig. 27.11) from enlarging tumors or lymph nodes or dynamic collapse of the airway as in case of tracheal bronchial malacia. The rigid bronchoscope is an excellent tool for the deployment of both self-expanding and silicone stents. The trachea and left mainstem bronchus are the most amenable airways for stenting because of their length and lack of branching airways. The right bronchial tree is more complex with very short distances between the main carina, right upper lobe, bronchus intermedius, and the right middle lobe. Placement of stents in the right bronchial

tree must be placed with great caution to avoid obstructing viable and patent airways. The rigid bronchoscope and its large working lumen allow the operator the greatest diversity of stents for deployment. Large silicone stents including Y stents can only be placed via rigid bronchoscopy. For deployment of stents in the left and right mainstem bronchi, remember the tips described under the techniques heading for manipulating the barrel of the scope into the appropriate airway.

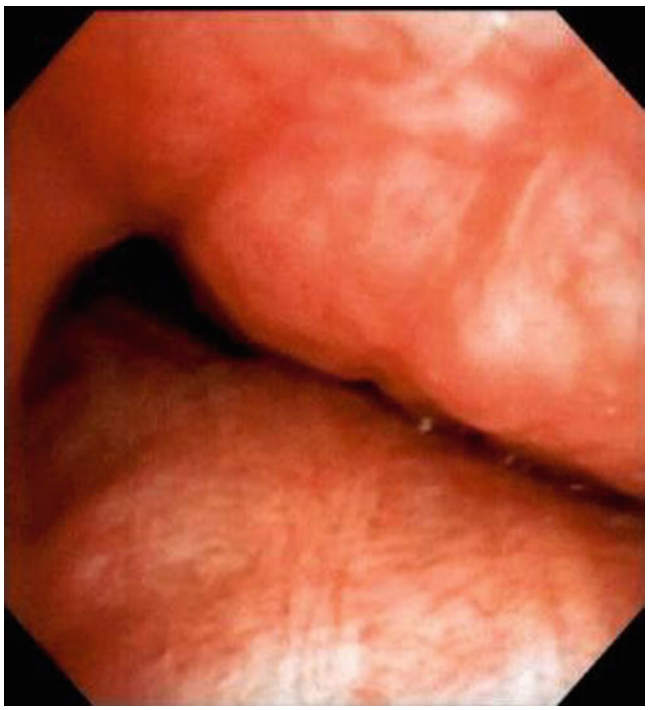


Fig. 27.11 Extrinsic airway compression. Mediastinal tumor compressing the right mainstem bronchus

Foreign Body

There is no body of literature comparing rigid bronchoscopy to flexible bronchoscopy for foreign body extraction from the airway. Although bronchoscopy has no effect on the acute event of foreign body aspiration, it is clear that the advent of bronchoscopy has positively impacted the subacute and chronic sequelae associated with airway foreign bodies. These are respiratory distress, obstructive pneumonia, and lung abscess. Jackson reported in 1936 that the mortality associated with foreign body aspiration dropped from 24% to 2% with a 98% success rate of foreign body extraction using his bronchoscope and graspers. The nature of aspirated foreign bodies has certain geographic and cultural variability. The most cited foreign body aspirations are vegetable matter, peanuts, or bones. The most common age groups for foreign body aspiration are children under the age of 3 and adults in the sixth and seventh decades of life. The most common anatomic site for aspirated foreign bodies in adults is the right bronchial tree due to its angle off the trachea. A unique form of airway obstruction is mucous impaction obstructing a silicone or expandable stent (Fig. 27.12). The obstruction is often waxy and defies conventional extraction with biopsy forceps. The cryoprobe is well suited to removing semisolid and solid airway obstructions freezing the often waxy mucous into a firm ball and extracted. In cases of impending respiratory distress from stent occlusion, the rigid scope can be used to remove the occluded stent, and simultaneously stent open the airway in preparation for a new stent deployment.

The rigid bronchoscope has been supplanted by flexible bronchoscopy in many respects, but there remains a significant role for rigid bronchoscopy in foreign body removal. In the Mayo Clinic case series of foreign body aspiration, rigid bronchoscopy was successful in 43 of 44 adult patients (98%), including six out of seven instances where flexible bronchoscopy failed to retrieve the foreign body. In comparison, flexible

Fig. 27.12 Self-expanding stent obstructed with waxy mucous impaction

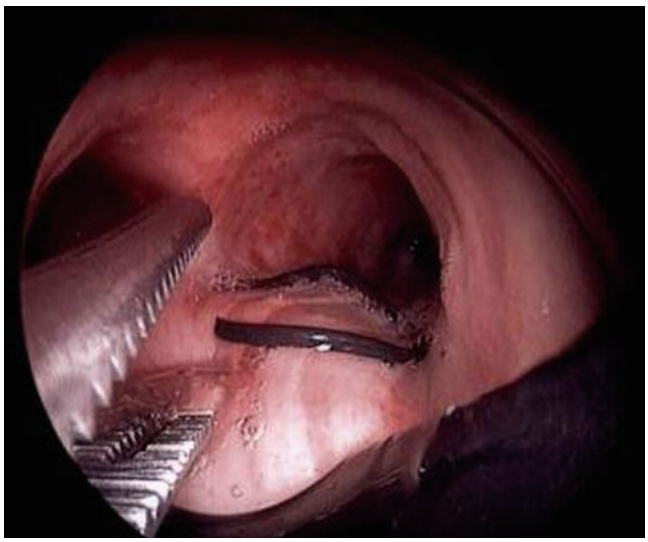


Fig. 27.13 Large rigid telescopic biopsy forceps for foreign body removal

bronchoscopy was successful in 14 of 23 patients (60%). It is reasonable to initially attempt foreign body extraction with the flexible bronchoscope in the stable patient, but rigid bronchoscopy is a useful adjunct, and prompt conversion to rigid bronchoscopy may save the patient from multiple interventions, obstructive complications, or even the need for surgical intervention. The advantage of the rigid bronchoscope is the diameter of the working channel and the larger scale of the working instruments (Fig. 27.13). This gives the bronchoscopist the ability to manage foreign bodies of different size, shape, and texture. The large scale of the working instruments allows for greater ease of grasping all or fragments of the foreign body and more rapid removal. It is critical to understand that the luminal diameter of the rigid and flexible bronchoscope does not dictate the size of the foreign body which can be removed. The luminal diameter of the scope dictates only the size of the working instrument which will grasp and manipulate the foreign body. The foreign body, the grasper, and the scope (both rigid and flexible) can be removed en masse if necessary to recover the foreign body. In cases of unstable airway due to foreign body aspiration, rigid bronchoscopy is the first tool of choice for extraction and management. In cases of critically unstable airways secondary to a foreign body, flexible bronchoscopy risks converting a tenuous airway to an occluded airway with fewer options for therapeutic manipulation.

Hemoptysis

Massive hemoptysis is one area in which there is little disagreement regarding the value of rigid bronchoscopy in salvaging a threatened airway and providing the quickest and most reliable localization of bleeding and control of the airway.

The goals in managing massive hemoptysis are securing the airway, identifying and isolating the bleeding source to prevent soiling of the unaffected lung, and facilitating cessation of bleeding.

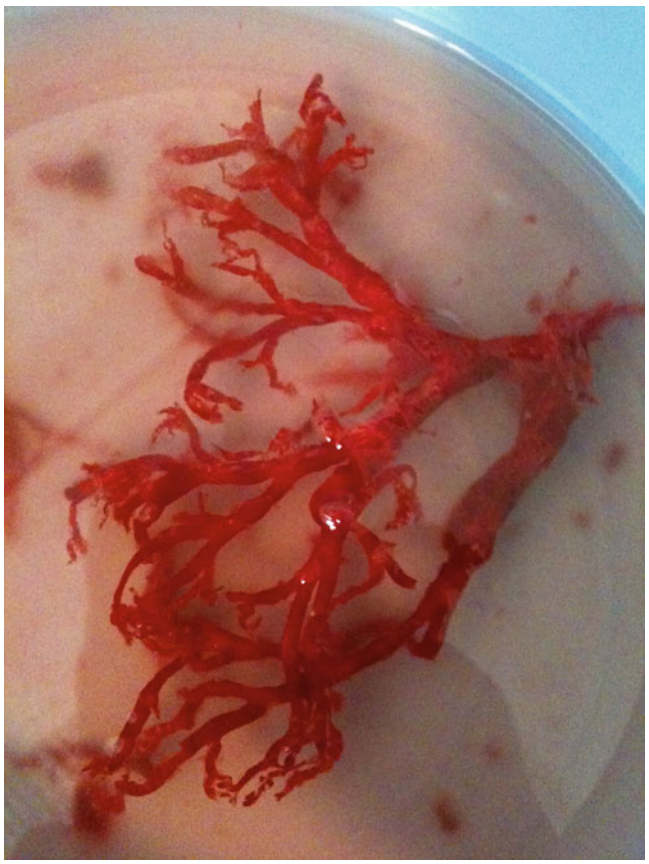


Fig. 27.14 Blood and fibrin airway cast removed from the right bronchial tree in patient with hemoptysis. Airway cast removed en bloc using cryoprobe

Localization of non-life-threatening hemoptysis is best done employing the flexible bronchoscope. It is rapidly available, does not require general anesthesia, can be performed at the bedside, and allows for the most thorough airway survey. This rapid diagnostic survey helps with therapeutic planning. Diagnostic bronchoscopy should be done early, within 24 h of bleeding to maximize the chances of localizing or, at a minimum, lateralizing the bleeding source.

The primary limitations of flexible bronchoscopy are diminished visibility even in the presence of small volumes of blood, low suction capability, lack of airway control, and limited therapeutic tools available. In the presence of active bleeding, it may be very difficult for the flexible bronchoscope to adequately obtain and maintain a clear airway, limiting both the goal of airway control and bleeding localization. The number one priority in massive hemoptysis is airway control and the principle of ABC's (airway, breathing, circulation) must be followed. The danger of hemoptysis is not blood loss but rather respiratory failure as blood and fibrin fill the bronchial tree (Fig. 27.14).

Rigid bronchoscopy affords the operator the greatest array of therapeutic tools as well as the greatest suctioning capacity while maintaining a stable airway and optimal visibility. The greatest advantage of rigid bronchoscopy in the setting of massive hemoptysis with respiratory embarrassment is large-bore suctioning. For bleeding lesions in the proximal airways, the rigid bronchoscope itself can be used to provide direct mechanical tamponade or directed placement of a balloon-occlusive device. The desire to perform a flexible bronchoscopy should not delay transfer to the operating room for a more definitive endoscopic approach.

Contraindications

There are very few absolute contraindications associated with rigid bronchoscopy. Patients with contraindications to general anesthesia like unstable coronary syndromes need to undergo a risk assessment to determine whether and when to proceed with the procedure. Other concerns are anatomic. Patients who cannot withstand hyperextension of the neck or rotation of the neck due to a fused or unstable cervical spine should not be considered for rigid bronchoscopy. Patients with unstable midline facial fractures should also avoid rigid bronchoscopy. Rigid bronchoscopy is a therapeutic tool, and careful clinical judgment and a risk-benefit assessment must always be applied to decision making.

Conclusion

Rigid bronchoscopy remains the technique of choice for complex airway pathology. The rigid bronchoscope allows the proceduralist to secure the airway, access the pathology, and intervene using a single instrument.

Rigid bronchoscopy should be considered the primary tool in managing central airway obstruction either from intrinsic pathology or extrinsic compression as well as managing massive hemoptysis and critical foreign body obstruction.

Management of critical airway pathology should involve a multidisciplinary approach involving surgical, radiographic, anatomic, and endoscopic considerations. The capability to safely do rigid bronchoscopy is critical to any complex airway program.

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Metallic Stenting

28

Mark Slade

Introduction

Metallic stenting is one of the most widely used techniques in interventional pulmonology. When employed for the management of malignant airway obstruction, the advantages of metallic over silicone stents largely outweigh the drawbacks, and in particular, modern self-expanding metallic airway stents (SEMAS) can be deployed easily via flexible bronchoscopy alone. Correctly employed, SEMAS insertion can be one of the most satisfying procedures in bronchoscopy, producing immediate and significant patient benefit. Importantly, however, while insertion may be straightforward, experience and judgment are required in patient selection and the management of complications. Metallic stents can be extremely difficult to remove, so they should only be employed when the benefits clearly outweigh the risks. The author has become more conservative in his use of metallic stents as his experience of interventional bronchoscopy has grown. It is the aim of this chapter to provide the reader with the knowledge needed to place the right stent in the right patient at the right time, in a manner that minimizes the risks of complication.

Some History

The first description of an entirely endoluminal airway stent, inserted endoscopically, was by Jean-François Dumon in 1990.

From early descriptions in the late 1980s, a large number of different metallic airway stents has been developed. They fall into two main types – those that are expandable but require dilatation to their final diameter and are deployed over a balloon and those that are self-expanding. The first metallic stents were made from stainless steel or tantalum, but these metals have been almost completely replaced by nitinol as the material of choice. Many of the early metallic stents are now considered obsolete.

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Expandable Metallic Stents

These include the Palmaz stent, made from a tube of stainless steel and rendered expandable by a series of longitudinal slits, and the Strecker stent, knitted from tantalum, a hard metal characterized by extreme resistance to corrosion. Both Palmaz and Strecker stents are compromised by their plastic rather than elastic property, which means that they can be collapsed by a single powerful cough. Neither stent was primarily designed for use in the central airways. They are now rarely used for tracheobronchial stenting, except when particularly small stents are required in children.

Self-Expanding Metallic Airway Stents

Self-expanding metallic airways stents (SEMAS) represent the industry standard for current airway stenting. Early SEMAS were made of stainless steel and expanded after deployment because of their geometric shape. An example, the Gianturco stent, is comprised of a collection of Z-shaped stainless steel wires. It was originally developed for use in the biliary tree. Although providing effective restoration of tracheobronchial patency, the Gianturco stent has a number of significant disadvantages. There are high pressure points on its perimeter, which prevent repositioning, even immediately after deployment, and which can lead to tracheobronchial perforation, with erosion into major vascular structures. In addition, the very open nature of the mesh of the Gianturco stent readily permits the ingrowth of tumor or granulation tissue. It is now rarely used.

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Currently Utilized Metallic Stents

Current SEMAS are made from nitinol, a nickel-titanium alloy that possesses remarkable properties that are ideally suited to stent design. Above a certain transition temperature (which corresponds in medical use to about 30 °C), nitinol is extremely elastic – it will permit a tenfold greater deformation than that tolerated by steel while still returning to its original shape. This is a property that it shares with many body tissues, including hair, cartilage, and bone. When cooled, however, it can be readily deformed, enabling the easy compression of a nitinol stent onto its delivery device during manufacture. The super-elasticity of nitinol at its working temperature means that nitinol stents are better able to conform to complex stenoses and to deform during coughing yet return promptly to shape, without compromising their resistance to radial compressive forces.

Figure 28.1 shows some currently used metallic airway stents. The current industry-standard SEMAS is the Ultraflex (Boston Scientific). This is knitted from a single strand of nitinol, and the nature of its mesh permits ready deformation to conform to complex, asymmetric stenoses. In the author's experience, Ultraflex stents are significantly less likely to fracture or migrate than other metallic stents (unpublished data). The Ultraflex is held compressed on its delivery device by a silk thread, wound round the stent and retained by a series of crochet knots in a linear pattern. The thread is pulled, releasing each knot in turn, during deployment. For tracheobronchial stents, a distal-release mechanism is usually chosen, which means deployment can be observed endoscopically. The stent remains attached to its delivery catheter until release is complete, permitting adjustments to positioning during the deployment process. Stents whose release occurs proximally to distally are also available. One disadvantage of the Ultraflex delivery system is that the external silk thread makes its surface rough and can cause bleeding from endobronchial tumor surfaces when it is passed into a tight, mixed stenosis.

In common with several other SEMAS, the Ultraflex has nylon loops or sutures, tied with a knot, running circumferentially at each end of the stent. These can be grabbed with forceps to permit stent repositioning (see Figs. 28.1, 28.2, and 28.3). Until recently, the loop was the same color (black) as

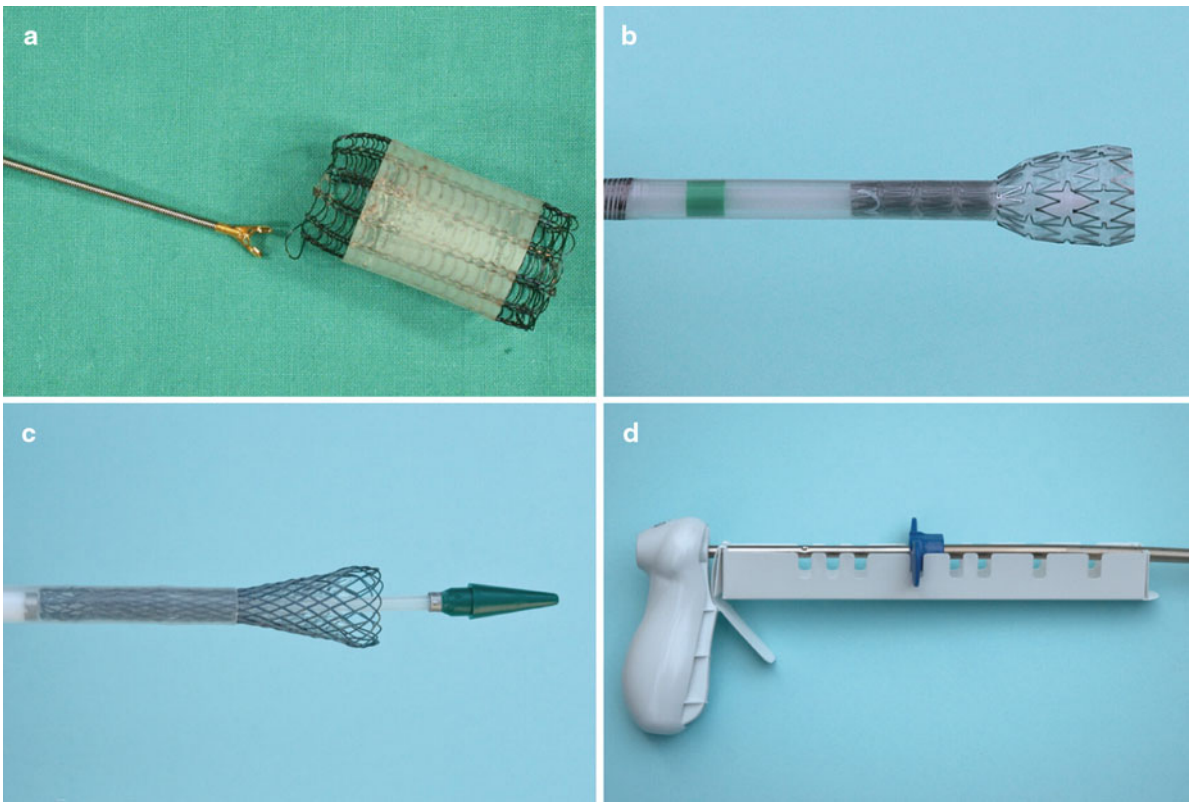

Fig. 28.1 Some self-expanding metallic airway stents in current use. *Top left*: a covered Ultraflex stent, showing the technique of grabbing the suture wound circumferentially around the proximal end of the stent. The suture material is now green in color, not black as shown here. *Top right*: an Alveolus AERO fully covered stent, half-deployed. The green marker corresponds to the proximal end of the stent in normal use. A blue suture is just visible through the external catheter at the proximal end of the stent. *Bottom right*: the deployment mechanism of the Alveolus AERO stent. After removing the white cardboard protector, the blue trigger is gradually moved proximally to deploy the stent. *Bottom left*: a part-deployed Micro-Tech stent, which also has a clear plastic outer sheath (Courtesy of Dr. Mark Slade.)

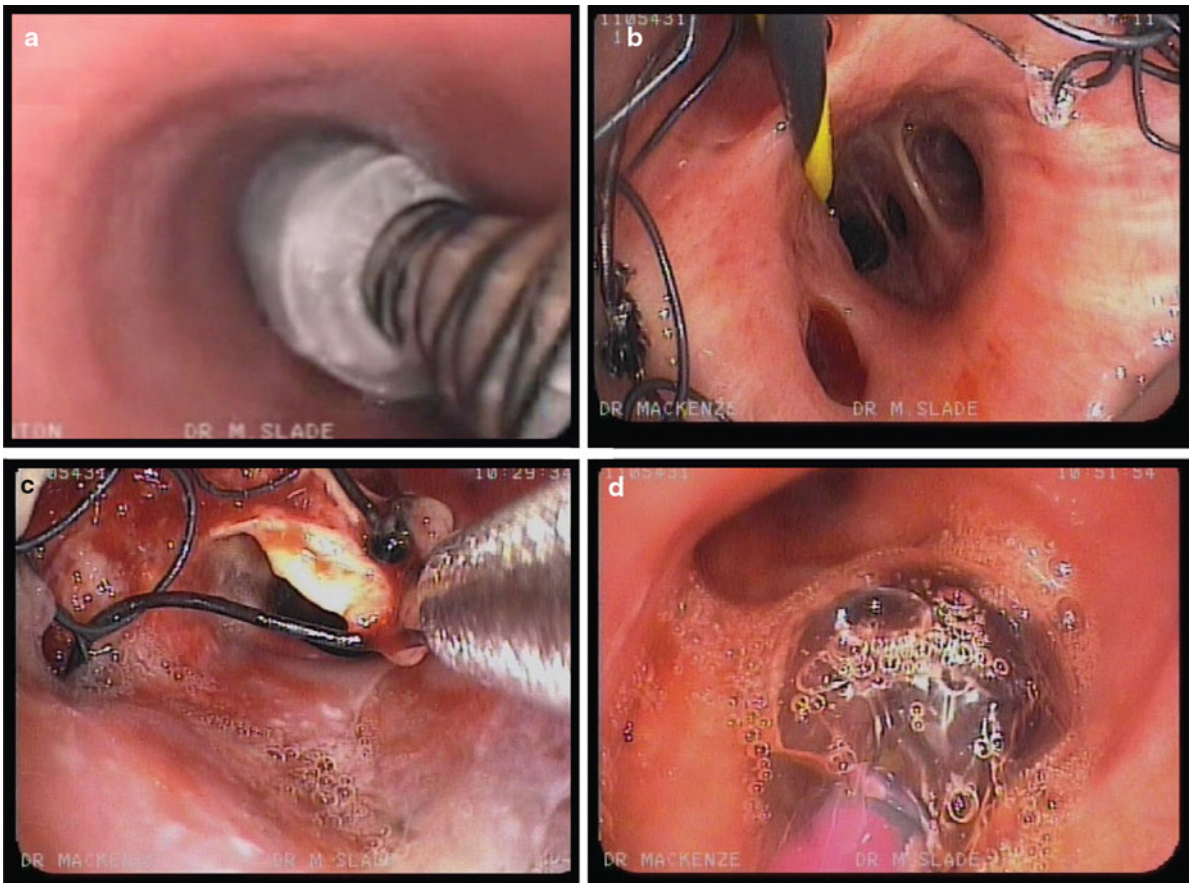

Fig. 28.2 Deployment and repositioning. *Top left*: a tracheal stent during deployment, illustrating endoscopic confirmation of stent positioning and distal to proximal release. *Top right*: confirming satisfactory distal position of a right main bronchial stent at middle lobe take-off. *Bottom left*: attempted distal repositioning of a stent by grabbing distal suture. *Bottom right*: post-deployment balloon dilatation of a stent in right main bronchus (Courtesy of Dr. Mark Slade.)

the rest of the stent, making its identification endoscopically challenging, but recently a green filament has been used.

Other stents use an external clear plastic catheter to compress the stent in position on its delivery device. Such devices have the advantage that their external surface is smooth, which minimizes trauma to the bronchial walls. Examples of stents using this type of delivery system include the Niti-S, Micro-Tech, and Alveolus AERO (see Fig. 28.1). In these stents, deployment is achieved by the withdrawal of the outer catheter, while the delivery device is held stationary by its proximal end.

Covered SEMAS vary in the proportion of their length that is covered. Ultraflex always have at least 0.5 cm uncovered at each end, while Niti-S and Alveolus are entirely covered. Although in principle these distinctions may appear relevant if, for example, it is important to leave uncovered a lobar take-off, or when tumor ingrowth threatens the entire length of a main bronchus, in practice it is rare for the length of the covering to affect the choice of stent in the author's experience.

A Few Words Concerning the Literature and Terminology

At the time of writing, there have been no randomized controlled trials assessing the insertion methods, or clinical effectiveness, of metallic airway stents. The literature therefore comprises case series, expert reviews and consensus statements from groups of leading practitioners. Aspects of the practice of metallic airway stenting vary widely between practitioners and centers, and the lack of an established evidence base means that any advice offered about stent choice, patient selection, or deployment techniques will necessarily strike some readers as different or even wrong. I have tried, wherever possible, both to reflect the breadth of published practice but at the same time to keep discussion of different options appropriate and practical.

For the sake of brevity, I shall use terms such as "malignant central airway obstruction" to mean obstruction of the central airways caused by malignant disease, and "benign aerodigestive fistula" to mean one caused by benign disease.

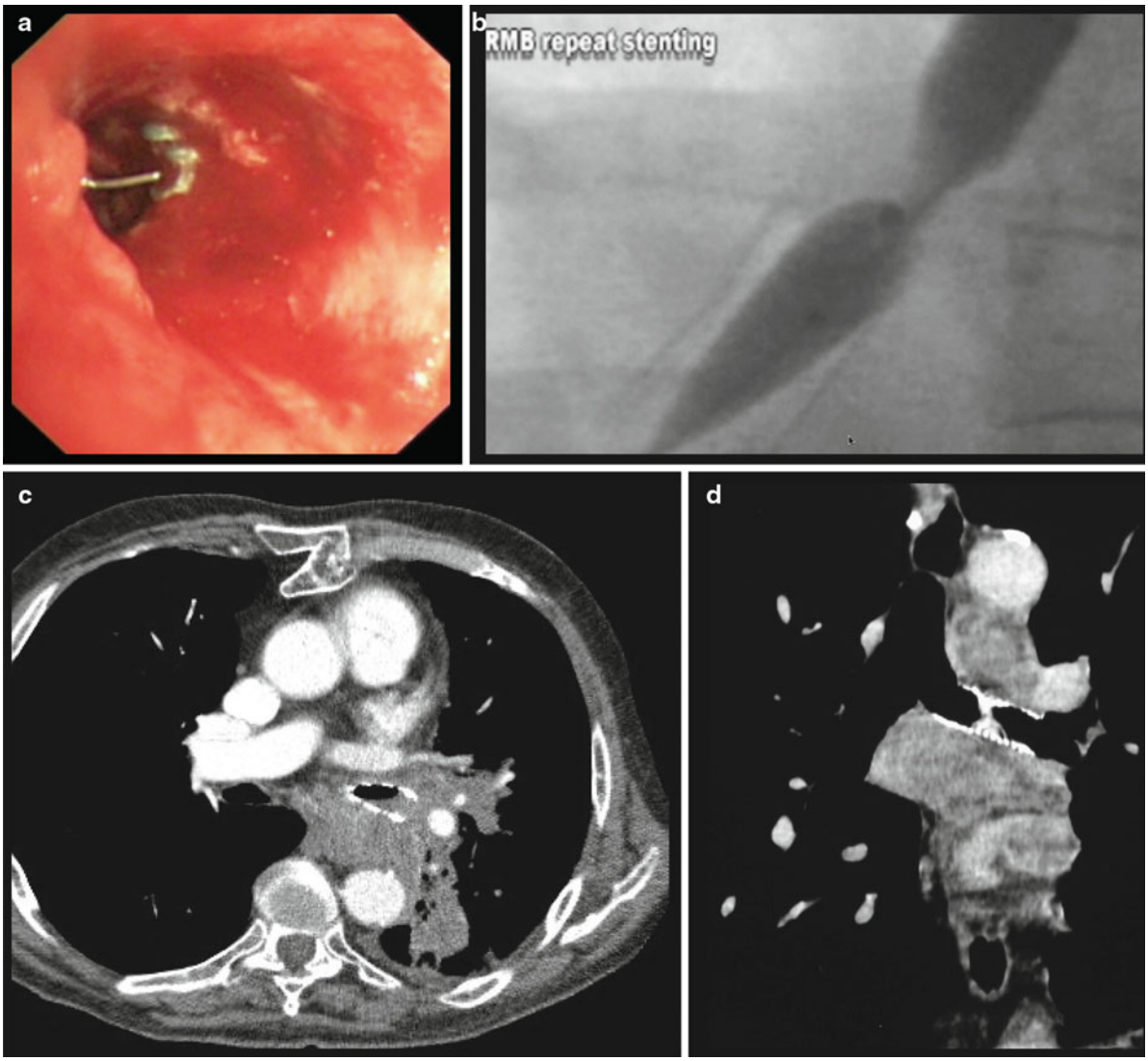

Fig. 28.3 Stent complications. *Top left*: a fractured strut of the proximal part of a left main bronchial stent is seen protruding into the bronchial lumen. This fracture was caused by an attempt to reposition the stent using forceps. The stent mesh was grabbed instead of the green suture, which is also just visible. *Top right*: a stricture has formed at the proximal end of an existing right main bronchial stent and is being ballooned. *Bottom left*: tumor ingrowth is visible into the distal end of a left main bronchial stent. *Bottom right*: a left main bronchial stent is obstructed by mucus impaction 6 weeks after placement (Courtesy of Dr. Mark Slade.)

This shorthand is not intended to imply that such a fistula, for example, is benign in its effect upon the patient.

Indications for Metallic Stent Insertion

The principal indications for metallic stent insertion are malignant central airway obstruction and management of malignant aerodigestive fistulae. Metallic stents are also used by some practitioners for the management of airway anastomotic complications following lung transplantation.

Management of Malignant Central Airway Obstruction

Metallic stents have been used in the management of all three types of malignant airway lesion: extrinsic, intrinsic, and mixed. Some authors favor covered metallic stents over uncovered whenever malignant central airway obstruction is the indication, even when the lesion is purely extrinsic, arguing that there is little downside risk to this approach and that a cancer cannot be relied upon not to invade the airway at a later date. A covered stent, however, cannot be deployed

across a patent airway side branch without the risk of causing post-obstructive pneumonitis. Choosing an uncovered stent in a situation where there is purely extrinsic compression of the target airway, for example, the right mainstem bronchus, but a patent side branch (say the right upper lobe in this example), minimizes the risk of occluding the side-branch airway. In the author's practice, the decision over whether to use a covered or uncovered stent is influenced by presence and patency of any airway side branches and the availability or otherwise of any effective anticancer treatment which may limit the risk of subsequent tumor ingrowth.

Some practitioners place a covered stent after debridement of intrinsic airway tumor, with the intention of maintaining airway patency by blocking tumor ingrowth. Others, of whom the author is one, prefer to use debulking therapies for intrinsic tumor, repeated as necessary and complemented by anticancer therapy where possible. This strategy avoids stent complications, which are described later, and in many cases it can be pursued for the remainder of the patient's life without requiring stent placement.

Malignant Aerodigestive Fistula

Fistulae between the esophagus and the trachea or main bronchi can complicate a number of thoracic malignancies, particularly esophageal carcinoma. Fistulae cause cough, fetor, and recurrent aspiration pneumonia, and survival is frequently very short. The goal of intervention is to seal the airway defect as completely as possible, to prevent further aspiration. Covered airway stents, esophageal stents, or both can be employed. Where the airway defect is situated close to the main carina, either in the distal trachea or the proximal portion of either main bronchus, a covered straight stent is rarely suitable, whether deployed in trachea or main bronchus, because the end of the stent will lie too close to the airway defect and tend to migrate into it. In this situation, a covered Y-stent is ideal. Carinal Y-stents are covered in detail in Chap. 30. Airway-esophageal fistulae are the subject of Chap. 41.

Posttransplant Anastamotic Complications

Metallic airway stenting has been employed to promote healing of anastomotic dehiscence following lung transplantation. Mughal and colleagues described 7 patients treated in this manner at the Cleveland Clinic, all of whom had life-threatening grade 3–4 bronchial dehiscence. A satisfactory final outcome was achieved in 6 of 7 patients, but only 3 of the 7 stents could be removed permanently, even though the authors' intention had been to place them temporarily. The management of disorders encountered after lung transplantation is covered in Chap. 45.

Benign Central Airway Obstruction

The temporary insertion of some types of metallic stent for the management of airway stenoses due to benign conditions is a controversial practice. In 2005, the Food and Drug Administration in the USA issued a medical device safety alert, warning against metallic tracheal stent use in this context, except where careful consideration had been given to alternative treatment options, including airway surgery and silicone stent insertion. The FDA further recommended avoidance of temporary deployment of metallic stents as a bridging therapy because subsequent removal can lead to serious complications. Perhaps as a consequence of this alert, there was a temporary, marked reduction in referrals for metallic stent removal at a major US interventional bronchoscopy center during 2006–2007. Alarmingly, however, such referrals had risen by 2008 to rates greater than those observed prior to 2005.

Patient Selection and Preparation for Stent Insertion

A successful and appropriate metallic stent insertion depends upon the stent being the right treatment both for the lesion and for the patient. The bronchoscopist should consider the following questions (adapted from Lee, Kupeli and Mehta 2010):

1. Is a stent the right treatment for this lesion? In particular, are there preferable alternative treatments (surgery, radiotherapy, systemic or debulking treatments for malignant disease; surgery, repeated dilatation, topical treatments for benign stenosis)?
2. Are the patient's condition and prognosis suitable both for the procedure and for meaningful palliation to be achieved?
3. What sort of stent, and of what length, diameter, and configuration, is required?
4. Is this the right hospital, team, and individual to insert it, or should I refer to a center with different expertise?
5. Does a stent need to be ordered for this procedure or is it in stock? It is advisable to have more than one stent available of the required dimensions in case the first one is mis-deployed or requires immediate removal for any reason.

Table 28.1 addresses the relative suitability of metallic airway stents in different situations. An example of an ideal patient for metallic stenting would be of good performance status but suffering from breathlessness on exertion, with

Table 28.1 Patient suitability for metallic airway stenting

	Best	Intermediate	Worst
Lesion	Purely extrinsic	Mixed	Purely intrinsic
Underlying disease	Malignant, poorly responsive to chemo/RT or no further treatment available	Malignant, responsive to chemo/RT	Benign
			Rapidly progressive, metastatic, or untreatable carcinoma (e.g., anaplastic thyroid carcinoma, small cell lung carcinoma not suitable for chemo/RT)
Site of lesion	Mid-trachea	RMB, RBI	Lobar
	Mid-LMB	Main carina	Distal LMB
			Distal RBI
Lobar take-off in stenosed segment	None	Present but occluded	Present and patent
Shape of stenosis	Dumbbell	Cylindrical	Conical
Length of stenosis	Short	Long, extending to proximal or distal airway branch	Long, involving distal airway branches
Severity of stenosis	50–95%	<50% or 95–99%	Total occlusion
			Minimal stenosis (e.g., post-ablation)
Distal airways	Patent on CT and endoscopically	Patent on CT, or filled with low-attenuation material	Not identifiable
Pulmonary artery branch accompanying airway	Patent	Narrowed	Occluded
Patient condition	Stable, breathless on exertion, ECOG 1–2	Stable but not breathless	Life-threatening CAO (very suitable but challenging)
		Significant cardiorespiratory instability	
Estimated life expectancy	3–24 months	1–3 months	< 1 month
		24–36 months	> 3 years

chemo chemotherapy, *RT* radiotherapy, *LMB* left main bronchus, *RMB* right main bronchus, *RBI* bronchus intermedius, *CAO* central airway obstruction, *ECOG* Eastern Collaborative Oncology Group

inoperable non-small cell lung cancer that has relapsed after treatment (say) with chemotherapy and radiotherapy. The patient would have a short, 80% stenosis of the midportion of the left main bronchus, just passable with a 5-mm flexible bronchoscope, and patent distal airways. Such a patient would have symptoms likely to benefit from stenting and a paucity of effective alternative treatments. She would be fit for the procedure and have a favorable lesion with no complicating factors, such as a lobar take-off within the treatment segment. No book can describe precisely what treatment choice to make in any possible situation, but in general decisions regarding stent insertion are influenced by the balance of favorable vs. adverse elements concerning the lesion and the patient, and the presence or absence of effective, alternative treatment options. The patient's life expectancy should neither be too short (futility, lack of meaningful palliation) nor too long (risk of fracture). Above all, stenting is a palliative procedure, and so the bronchoscopist should never have to persuade the patient to have a stent inserted. This last consideration is particularly important because some patients report few symptoms, even in the presence of apparently severe airway lesions. The temptation for the bronchoscopist is to intervene, especially if the airway lesion appears readily treatable. Caution is advised in such circumstances, however, because no risk is greater than the one that did not need to be taken.

Pre-procedure Patient Assessment

The work-up for metallic stenting necessarily depends upon the patient's condition. In emergent near-complete tracheal obstruction, intubation and immediate rigid bronchoscopy by the most experienced available practitioner without any pre-procedure work-up may be entirely appropriate. Almost always, however, in addition to a history and physical examination and standard pre-bronchoscopy tests, it is appropriate to request airway CT scanning, spirometry, a flow-volume loop, and an assessment of breathlessness, such as the MRC or Borg dyspnea scores. Some operators favor a prior flexible bronchoscopy to assess the lesion anatomy. Once these tests have been completed, it will often be possible to arrive at a complete specification for the desired stent. Airway CT scanning, particularly if carried out on a high-speed multidetector scanner, can be used to create multiplanar reformat and virtual bronchoscopy images. These enable the diameter of the stenosed segment and, if present, the adjacent normal airway to be estimated. Where the target bronchus has no segment of normal caliber throughout its length, estimates of its usual caliber can be obtained by measuring the corresponding contralateral airway. Images displayed on lung window settings provide a more accurate impression of the likely endobronchial appearances. Dynamic CT images, obtained during expiration, can further define regions where dynamic airway

collapse occurs, sometimes as a consequence of the destruction of airway cartilage by underlying tumor. Standard flexible bronchoscopy provides visual assessment of the severity and length of airway stenoses, the patency of any adjacent lobar take-off (particularly the right upper lobe), and the presence or absence of endobronchial tumor. In addition, the relationship of the stenosed segment to distal or proximal airway branches can be precisely assessed. In lower-volume centers, performing a flexible bronchoscopy prior to stenting permits a stent of the required size to be ordered for the procedure, thereby minimizing the requirement to keep an extensive stock of stent sizes. For many straightforward cases, CT scanning, lung function, and clinical assessment will be sufficient to enable satisfactory treatment planning, with an on-table flexible bronchoscopy providing additional information and enabling final stent selection and sizing. This approach has the benefit of simplicity and economy but relies upon the availability of a full range of stent sizes and types, since the final selection is made during the procedure.

Miyazawa and colleagues assessed the impact of a more sophisticated pre-procedure assessment in patients with lung cancer requiring airway stenting. Dynamic airway CT scanning, flow-volume loops, endobronchial ultrasound (EBUS) and ultrathin flexible bronchoscopy were performed before and after stenting in 64 patients. These techniques were combined to allow the identification of specific choke points (wave-speed flow-limiting segments) within the airways. The CT scans were performed at end-expiration, with 3D airway reformats. Characteristic flow-volume loop appearances could be identified for lesions in three locations: the trachea, around the main carina, and confined to the main bronchi, with more complex stenoses exhibiting a combination of appearances. EBUS was used to assess the integrity of underlying airway cartilage. In some patients, this was found to have been destroyed by extrinsic tumor over a length of airway wall greater than that affected by the stenosis itself. EBUS allowed the authors to select longer stents in this situation, to prevent dynamic airway collapse of the damaged airway. Ultrathin bronchoscopy was employed to identify choke points directly. In this study, a combination of silicone and metallic stenting was employed. Using these pre-procedure assessments, patients with tracheal (n = 20), carinal (n = 16), and bronchial lesions (n = 18) were satisfactorily treated with a single stent procedure alone, with significant improvements in lung function parameters and WHO dyspnea grade. In patients with complex stenoses affecting more than one region of the tracheobronchial tree, however, migration of the choke point after an initial stent procedure was observed. In this group of patients, even though significant improvements in lung function and dyspnea scores were observed after a single procedure, there was a further incremental and statistically significant improvement in each of these parameters after a second stent procedure, in which stent deployment was targeted at the migrated choke points identified by the detailed assessment described. The results of this study are worth emphasizing, because many bronchoscopists might have congratulated themselves after achieving the more modest patient benefits demonstrated after the first stent procedure in these complex lesions. This study provides evidence in favor of the proposition that all such patients should be treated in centers with access to a full range of advanced bronchoscopic techniques and that there is a lot more to successful stenting than knowing how to deploy the stent.

Selection of an Appropriate Airway Stent

Although it may appear facile to point out, it is worth emphasizing that the length, diameter, and type of airway stent should be chosen to meet the patient's needs, not the resources or ability of the bronchoscopist. The relative ease of deployment of metallic stents makes their use accessible to practitioners who lack training in rigid bronchoscopy and silicone stent insertion. It is important for such individuals (of whom the author is one) both to know their limitations and to be aware of the capabilities of others. This point is illustrated by the findings of Alazemi and others who were referred 46 patients for removal of 55 metallic airway stents, 80% of which had been placed for benign conditions, for which silicone stenting would have been more appropriate. Stent removal proved complex, hazardous, and costly.

The pros and cons of metallic vs. silicone stenting are summarized in Table 28.2. In general, the benefits of metallic stenting outweigh the disadvantages in the case of malignant central airway obstruction. To minimize the possibility of tumor ingrowth, covered stents are almost always chosen in this situation, except when the airway compression is purely extrinsic, and it is necessary to stent across a patent lobar bronchus (usually the right upper lobe). The stent diameter is chosen to be approximately 2 mm greater than the normal diameter of the target airway, to reduce the possibility of stent migration. In the main bronchi, this can be estimated from CT scanning as detailed above and will usually be in the range 10–14 mm. The same procedure is used for the trachea, except that metallic tracheal stents are usually 18–20 mm in diameter, whereas the normal male trachea may be up to 24 mm. This disparity does not cause problems in practice, however, because the stent will be held in place by the stenosed segment.

The length of the stent is usually chosen to extend, if possible, at least 0.5 cm farther both proximally and distally than the stenosed segment. This length is commonly estimated from flexible bronchoscopy, by passing the bronchoscope to the distal extent of the lesion, marking the position

Table 28.2 A comparison of silicone and metallic stent properties

Quality	Silicone stent	Metallic stent
Ease of deployment		
Flexible bronchoscopy	No	Yes
Moderate sedation + topical anesthesia	No	Yes
Day-case procedure	Usually not	Yes
Complications		
Granulation tissue in-/overgrowth	Little	More
Tumor in-/overgrowth	Only at ends	Yes in uncovered portion/stent
Migration	Significant	Less common, except fully covered stents
Fracture/degeneration	Very rare	Significant with longer follow-up
Infection	Uncommon	More common
Tracheobronchial perforation	Very rare	Possible, more common with stiffer stents
Mucus impaction	Common	Uncommon
Material properties		
Modifiable	Easily	No
Ease of repositioning	Easy	Immediately – fair
		Subsequently – not advised
Ease of insertion	Fair	Good
Conforms to complex stenoses	No – single diameter	Yes
High internal-external diameter ratio	No	Yes
Elasticity during, e.g., coughing	Poor	Excellent – nitinol
		Fair – other metals
Permits mucociliary clearance	No	Yes – uncovered stent
		No – covered stent
Cost	Less	More

Table 28.3 Common variations in metallic stent insertion techniques

	Possible procedural variations
Technical element	
Anesthesia	General anesthesia
	Moderate sedation and local anesthetic
Bronchoscope	Flexible
	Rigid
Airway adjunct	Rigid bronchoscope
	Endotracheal tube
	Laryngeal mask
	None
Stricture dilatation	Balloon
	Jackson dilators
	None
Stent placement	Over guidewire placed via flexible bronchoscopy
	Over guidewire placed via rigid bronchoscopy
	Stent placed directly via rigid bronchoscopy
	Stent placed directly *over* flexible bronchoscope (Alveolus DV system)
Deployment visualization	Direct via flexible bronchoscopy
	Direct via rigid bronchoscopy
	Indirect via fluoroscopy
	Combined bronchoscopic and fluoroscopic
Post-deployment dilatation	Balloon dilatation
	Forceps dilatation via rigid bronchoscopy
	None

on the scope where it emerges from the nose or mouth, and then withdrawing it until the proximal extent of the lesion is reached. The displacement of the bronchoscope is then measured between the two points to estimate the required stent length. Usually, a 4-cm stent is appropriate for the left main bronchus, and 2–4-cm stents for the right main bronchus, depending upon the patency or otherwise of the right upper lobe. Stent length can also be estimated from coronally reformatted CT images. Prior assessment using radial EBUS may prompt the selection of a longer stent to cover areas of cartilage damage, as described above.

Insertion Procedure

There are many variations possible in the insertion procedure for metallic stents. These are in anesthesia, bronchoscope, airway management, type of airway dilatation, and visualization technique. They are summarized in Table 28.3. Among interventional bronchoscopy practitioners with access to a full range of techniques, stents are most commonly inserted using rigid bronchoscopy, general anesthesia, and direct endoscopic, rather than fluoroscopic, visualization. This setting probably offers the most rapid and controlled insertion, though trials comparing the safety, efficacy, and cost-effectiveness of different insertion techniques are currently lacking.

After appropriate patient assessment and consent, the insertion procedure begins with the induction of general anesthesia and muscle relaxation for rigid, or moderate sedation for flexible, bronchoscopy. The airway is then secured as desired.

Rigid Bronchoscopy

When performing stenting via rigid bronchoscopy, the target airway segment is assessed bronchoscopically and the luminal diameter maximized by tumor ablation and airway dilatation. The stent delivery device can then sometimes be passed directly into position via the bronchoscope, or alternatively a guidewire can be passed either directly or via a flexible bronchoscope passed through the rigid scope. If a flexible bronchoscope is employed, it must be removed again

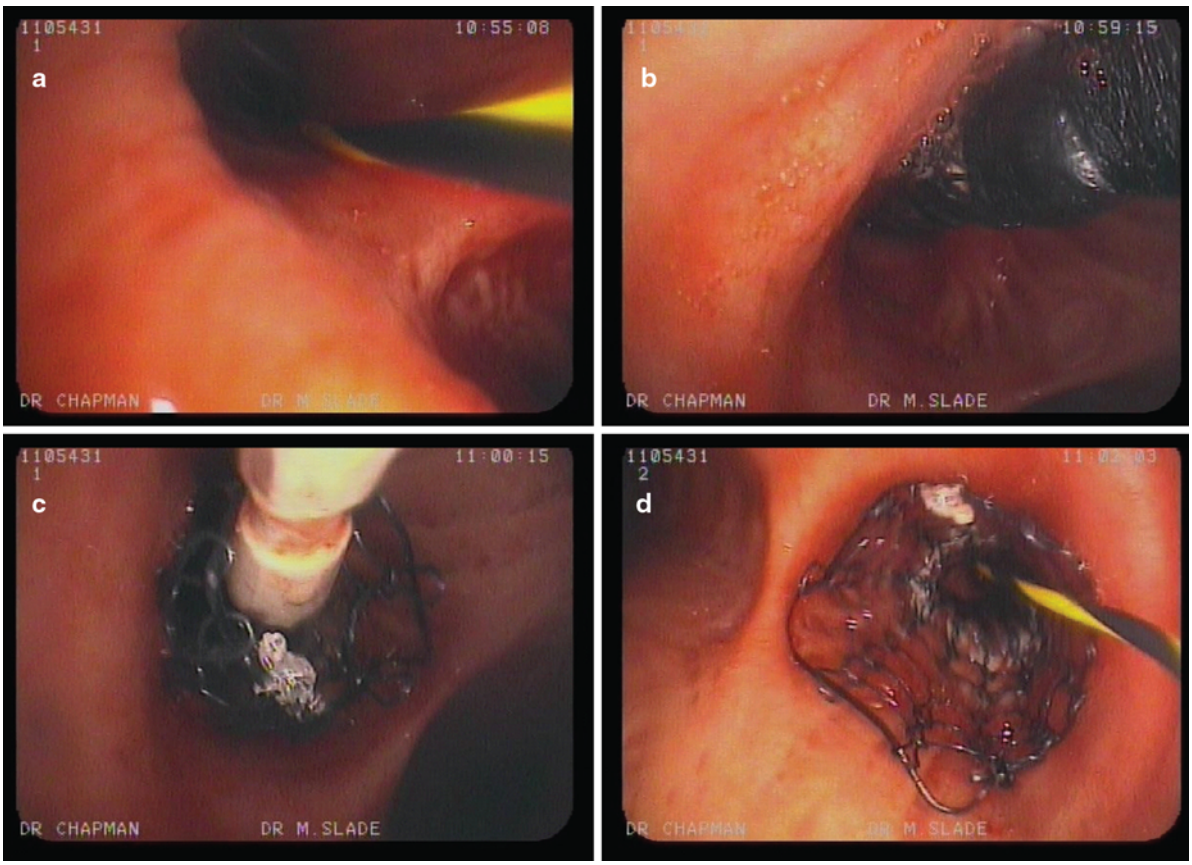

Fig. 28.4 Stent deployment in the right main bronchus. *Top left*: a guidewire is passed. *Top right*: an Ultraflex-covered stent is passed over the guidewire, and the position of the proximal end of the stent is confirmed endoscopically. *Bottom left*: the stent has been released from the delivery device, which is carefully withdrawn with a twisting motion to ensure that it is free from the stent. Care is taken not to dislodge the newly released stent. *Bottom right*: the final stent position is checked endoscopically (Courtesy of Dr. Mark Slade.)

over the guidewire. The stent delivery device can then be passed over the guidewire. Guidewires suitable for stent deployment have a floppy distal end, to minimize the risk of pneumothorax, but the remainder of the wire is relatively stiff, which limits any tendency of the delivery device to kink during passage into position. If the airway lumen permits, the stent is observed during deployment by positioning a thin flexible bronchoscope or rigid optic close to the distal end of the stent as deployment begins. The scope is then withdrawn proximally so that both distal and proximal ends of the stent are observed to overlap the stenosed segment. In most instances, however, if the length of the stenosed segment and its relation to appropriate landmarks is known, then it is sufficient to visualize the correct placement of the proximal end of the stent, and thereby to infer the position of the distal end.

Flexible Bronchoscopy

The insertion procedure via flexible bronchoscopy has many similarities[1]. A typical deployment of an Ultraflex stent is shown in Fig. 28.4. After moderate sedation is established, an endotracheal tube (ETT) or laryngeal mask airway (LMA) can be inserted. It is usual to do so for tracheal stent insertion, but bronchial stents can be inserted in stable patients without an artificial airway. After the airway lumen is maximized by balloon dilatation and/or debulking, a guidewire is passed and the scope withdrawn over the wire. If an ETT is used, the scope can be reintroduced alongside the ETT and the stent delivery device advanced over the guidewire into position, which is verified bronchoscopically as above.

[1]Hautmann H, Bauer M, Pfeifer KJ, Huber RM. Flexible bronchoscopy: a safe method for metal stent implantation in bronchial disease. Ann Thorac Surg. 2000;69:398–401

Some practitioners use fluoroscopy alone to verify stent positioning prior to deployment. This technique requires the prior positioning of skin surface radiopaque markers corresponding to the desired position of proximal and distal ends of the stent. This is usually done by placing the flexible bronchoscope at each of these positions and screening. Endoscopic visualization is generally preferred over fluoroscopy, however, because it is more precise, easier to interpret, and not subject to image degradation if the bronchus is rapidly moving during coughing.

Dilatation Post Deployment

After deployment, metallic airway stents gradually enlarge to their final dimensions. This process may not be complete until 24–48 h have passed. Balloon dilatation may be employed within the stent to speed this process (see Fig. 28.2). Generally, this is done if there is a need rapidly to increase airway patency, or if there is any infolding of the stent that can occur with certain stent types. It may also be used to reduce the chance of stent migration by apposing the stent more firmly against the bronchial wall. It is the author's preference not to balloon a stent for three reasons: it is almost always unnecessary; it increases the cost of the procedure; and if the patient is breathing and coughing spontaneously, there is a risk of stent migration caused by the friction between the balloon and the stent.

Position Adjustments Post Deployment

Le mieux est l'ennemi du bon (Better is the enemy of good)

– Voltaire

Following deployment, minor adjustments to the stent position can be made by grabbing the proximal or distal suture present on most metallic stents and dragging the stent into the desired position (Fig. 28.2). It is much harder to move a stent more distally than more proximally. Initial malposition of the stent is more frequent when muscle relaxation is not used, because coughing during deployment can both transiently obscure the bronchoscopic view and change the relative position of stent delivery device and bronchial tree at the critical moment. The reader is advised against making fine adjustments to stent positioning post deployment, however, particularly in the spontaneously breathing patient. It is easy to make the situation worse: the patient may cough, the stent may be fractured by grabbing its mesh rather than its suture (Fig. 28.3), and the stent may be inadvertently removed. It is often better to accept a somewhat unsatisfactory deployment, and if necessary repeat the bronchoscopy in 48–72 h.

Post-procedure

Following stent insertion the patient is observed until ready for discharge. Chest radiography is recommended if there is persistent or violent coughing, to check for stent migration. It can also serve as a record of satisfactory placement. If the reestablishment of bronchial patency has liberated extensive, thick, or purulent bronchial secretions, it is the author's non-evidence-based practice to prescribe mucolytics and antibiotics.

The provision of a stent card or alert bracelet is recommended, detailing the size and location of the stent and providing advice and a telephone number for use in emergencies where intubation is contemplated.

Follow-Up

The only consensus regarding follow-up after stent insertion is that it should be done; timing and content of follow-up visits vary among centers, and there is little evidence upon which to base recommendations. It is appropriate to see all patients 1–4 weeks post-procedure to assess symptoms, lung function, and radiographic appearances. Assessment of quality of life with dyspnea scores (e.g., MRC or Borg score) and exercise performance by 6-min or shuttle walk testing are, in the author's opinion, the most helpful tests of response to treatment, but it is conventional in addition to document changes in FEV1, FVC, and flow-volume loop. Routine bronchoscopy post-procedure is practiced by some and can detect early complications such as mucus impaction and granulation tissue formation before symptoms arise. In the study of Miyazawa and colleagues, routine follow-up bronchoscopy was part of a management plan that led to successful, second stent procedures in a minority of patients with complex stenoses. It does, however, subject the patient to inconvenience, discomfort, and cost in what is intended as a palliative setting. Multidetector CT scanning detects the majority of stent complications and is appropriate in patients with symptoms warranting investigation.

Results

Metallic airway stenting for malignant central airway obstruction usually results in immediate and significant improvements in breathlessness and lung function. The literature is made up of case series, in which symptom outcomes are often ill-defined, and lung function assessments pre- and post-procedure are often not available either because no pre-procedure assessment could be performed (e.g., the patient was intubated) or because no follow-up data were available. Saad and colleagues described the results of metallic

airway stenting in 82 patients, of whom 50 had lung cancer. 72/82 patients had "symptomatic improvement after airway stenting." Breitenbucher and colleagues inserted 62 Ultraflex stents in 60 patients with malignant CAO. They observed that, "Successful reopening of the airways was noted in all patients." Paired spirometry results were available in 17 patients, for whom there was a 23% improvement in FEV1 from 1.45 +/− 0.48 to 1.78 +/− 0.62 L ($p = 0.003$). In this study 42/60 (70%) patients received chemotherapy or radiotherapy after stenting, and 23% developed a stent-related complication. It therefore remains possible for the stent skeptic to argue that most of the symptomatic benefit gained by the patients in this study could perhaps have been achieved by a treatment strategy involving chemotherapy and radiotherapy alone, which would have avoided all of the observed complications. Unfortunately, most experienced interventional bronchoscopists now believe that it would be unethical to randomize such patients into a trial of stenting plus anticancer treatment vs. anticancer treatment alone, so it is unlikely that the evidence for efficacy of airway stenting will strengthen significantly.

Complications

Complications of metallic stent insertion are frequent but usually not severe. They are summarized in Table 28.4 and illustrated in Fig. 28.3. Their frequency varies according to stent type, duration of post-stenting survival, and underlying disease. In a series in which 112 stents (80% Wallstents, 20% Ultraflex) were inserted in 82 patients (50 with lung cancer, 11 lung transplant, and 21 miscellaneous benign conditions) over a 6-year period, complications occurred in 47% of patients. By contrast, in patients treated with exclusively Ultraflex stents for malignant CAO, Breitenbucher and colleagues found complications in 23%, the commonest being mucus impaction (8%), granulation tissue (5%), tumor restenosis (5%), and migration (5%). Granulation tissue overgrowth at the ends of the stent is uncommon when stents are inserted for lung cancer, but occurred in about one in six patients treated for miscellaneous benign conditions or lung transplant anastomotic problems. It can be treated by cryotherapy or, for uncovered stents, by argon plasma coagulation. Infection, most commonly staphylococcal bronchitis, has been described with variable frequency but may rarely necessitate stent removal or lead to bronchial perforation and massive hemoptysis. Stent migration requiring removal is illustrated in Fig. 28.5, and iatrogenic stent fracture caused by grabbing the stent mesh, rather than its suture, is shown in Fig. 28.3.

Stent Removal

There is a joke told in Ireland of a city man who draws up his car at the roadside to ask a farmworker for directions to Balbriggan. The local man offers a series of instructions but ends by saying, "But if I were you, I wouldn't start from here." This folk wisdom neatly exemplifies how the experienced interventional bronchoscopist approaches metallic

Table 28.4 Metallic stent complications

Complication	Frequency	Treatment	Notes
Granulation tissue	4–25%	Cryotherapy	Commoner when mucosa normal
		Laser	Forms at ends of stent
		Argon plasma coagulation	
Mucus impaction	5%	Suction	Mucolytics, nebulized saline of unproven benefit
		Mechanical removal	
		Cryo-removal	
Infection	5–5%	Antibiotics	Commonly staphylococcal
		Rarely stent removal	May rarely lead to fatal hemoptysis
Tumor ingrowth	5–15%	Argon plasma coagulation	Not with fully covered stents
		Laser (care!)	
		Brachytherapy	
Migration	5–50%	Repositioning if early	Much commoner with fully covered stents
		Removal if late (>30 days)	Rare with uncovered stents
			Conical stenoses
Stent fracture	Variable	Removal if required and necessary expertise and equipment available	Increasing frequency with duration of implantation
			Commoner with more rigid stent types Occurred in 6/19 (31%) of Gianturco stents [Rousseau 1993]
Tracheobronchial perforation	Rare	Extremely difficult	Commoner with, e.g., Gianturco stents or other more rigid designs
		Stent removal if possible. Repeat stenting within existing stent	

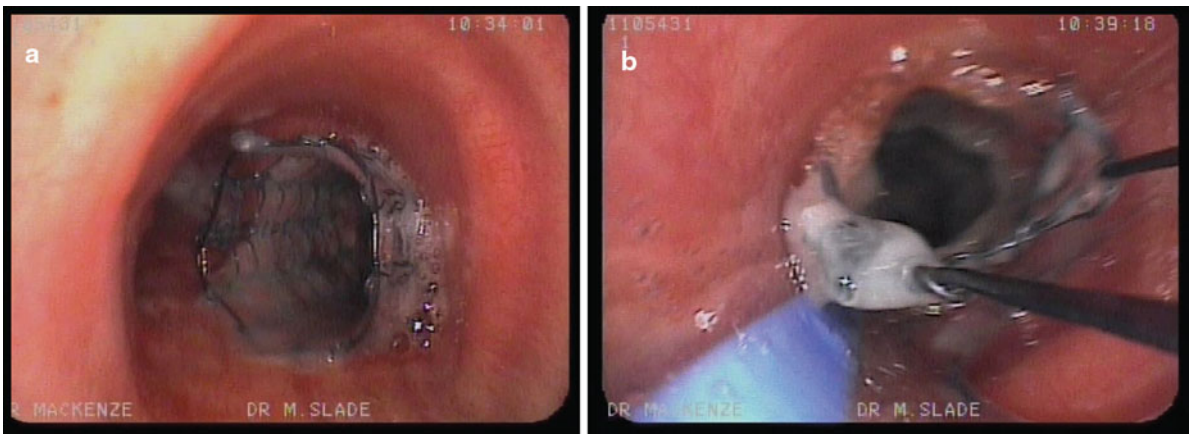

Fig. 28.5 Stent removal. An Ultraflex-covered stent has migrated within 48 h of placement in the right main bronchus (*left*). It is removed by pulling it into an endotracheal tube using forceps to grab the proximal stent suture (*right*). This has the effect of pulling the cylindrical stent into a more conical shape at its proximal end, facilitating removal (Courtesy of Dr. Mark Slade.)

stent removal. Depending upon the stent type and the presence or absence of granulation tissue or tumor ingrowth, metallic stents may remain relatively easy to remove for roughly 30 days, especially if the reason for removal is migration. An example of the removal of a migrated, covered Ultraflex stent from the right main bronchus is illustrated in Fig. 28.5. In this case, the stent was pulled using its proximal suture into an ETT, and then the ETT, bronchoscope, and stent were together removed from the trachea. Metallic stents that have been in situ for longer or have fractured or caused bronchial perforation, however, may be extremely difficult, hazardous, and costly to remove. Removal should only be attempted in centers with considerable expertise in interventional rigid bronchoscopy, thoracic surgery, and critical care. For conflicting descriptions of the difficulties of stent removal, see Noppen et al. (2005) and Alazemi and others (2010). Alazemi and others found that the hospital and ICU bed-days, and total costs, were significantly higher for stent removal from patients with benign when compared with malignant conditions. They further found that, after a temporary reduction in referrals for SEMAS removal from patients with benign conditions in 2006–2007, such referrals increased dramatically in 2008–2009, implying that the effect of the FDA advisory on SEMAS use had only a temporary impact upon practice patterns in the USA.

The technique for stent removal using rigid bronchoscopy is described by Lunn and others (2005). In brief, an airway CT and flexible bronchoscopy are first performed to assess the anatomy of the airway, the condition of the stent, and the relationship of vascular structures to the airway wall. Rigid bronchoscopy is performed with jet ventilation through an open airway. In some patients treatment of granulation tissue with argon plasma coagulation or electrocautery is required. If necessary, the airway and stent are dilated with a balloon to increase the lumen in which to work. The rigid bronchoscope is positioned at the proximal end of the stent, and then the stent carefully separated from the airway wall by using the bronchoscope tip, Jackson dilators, or optical forceps. Rigid alligator forceps are used to grab the stent and then rotated to wrap the stent as much as possible around the forceps, before gentle traction is applied in an effort to remove all or part of the stent. Remaining stent fragments or wires are then removed piecemeal until removal is complete or airway edema forces termination of the procedure. Restenting of the airway with a silicone prosthesis may be required in about half of cases.

Summary

Metallic airway stents have an important role in interventional bronchoscopy and can provide rapid and effective relief of breathlessness and other symptoms caused by malignant central airway obstruction. Lesions wholly due to endobronchial tumor are better treated with repeated tumor debulking. Metallic stents are not recommended for use in benign airway diseases. Their use is associated with a range of complications. Removal of metallic stents more than 30 days after insertion is challenging and hazardous and should only be attempted in well-equipped centers with extensive expertise in interventional bronchoscopy, where skilled help from colleagues in anesthesia, critical care, and thoracic surgery is rapidly and continuously available.

Acknowledgments The author would like to thank Laurence Pengelly who provided the stent photographs reproduced here. Gerry Slade, an experienced bronchoscopy nurse, provided expert advice, support, and encouragement.

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Endobronchial Silicone Stents for Airway Management

29

Hervé Dutau

Introduction

The main purpose of stents designed for use in the central airways (trachea, mainstem bronchi and in select cases lobar bronchi) is to restore patency of the airway to as close to normal calibre as possible. These stents may be useful in airway obstruction leading to the onset of debilitating symptoms such as dyspnea whether the obstruction is due to a malignant or benign process either intrinsic or extrinsic to the airway. They may also be used in order to cover fistulas between the central airways and local structures such as the mediastinum or oesophagus.

The Montgomery T-tube was the first silicone stent available to re-establish airway patency post-operatively for tracheal disease. In the late 1980s, Dr. J.F. Dumon created the first strictly endoluminal stent specifically designed for airway use.

His achievements gave the discipline of interventional bronchology a very important momentum. Suddenly, pulmonologists could approach and treat central airway diseases that had formerly been considered either completely untreatable or treatable only by extensive surgical procedures. Dumon silicone stents rapidly became popular. The initial airway stent had a simple design consisting of a silicone tube with small studs on the external surface to reduce migration (Fig. 29.1). They have become the de facto gold standard for the treatment of benign and malignant stenoses over the past 10 years.

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Available Silicone Stents

Dumon Stent

Many silicone stents are commercially available, although the Dumon stent (Tracheobronxane®, Novatech, La Ciotat, France) remains the reference standard as it is the most commonly placed stent worldwide. There are two specific designs: straight and Y (for disease involving the carina, to be treated in another chapter of this book). Stents are available in various lengths and diameters to accommodate both paediatric and adult indications (Fig. 29.2). The largest available external diameter is 20 mm. For irregularly shaped stenoses, i.e. those with marked reduced central airway calibre as compared to the extremities, specialised hourglass-shaped stents are available (Fig. 29.2). These hourglass-shaped stents are particularly useful in cases of short benign tracheal disease. The currently available stents are either made of transparent silicone (non-radio-opaque) or made of silicone melted with barium sulphate (white colour) (radio-opaque) (Fig. 29.2). Soon, the new generation of transparent Dumon silicone stents (Tracheobronxane®, Novatech, La Ciotat, France) will have gold markers included in their studs to provide radio-opacity. The transparent Dumon stent offers the possibility to visualise the mucosa behind its wall.

Dumon stents can be inserted in many different ways. Ideally, it is inserted through a dedicated rigid bronchoscope even if it is feasible using a flexible scope.

The commercialised introducer set includes a loading tool and a pusher (Fig. 29.3). A Dumon stent can be repositioned, removed and replaced at any time with ease using standard grabbing forceps. On-site modification of these stents is technically possible (Fig. 29.4).

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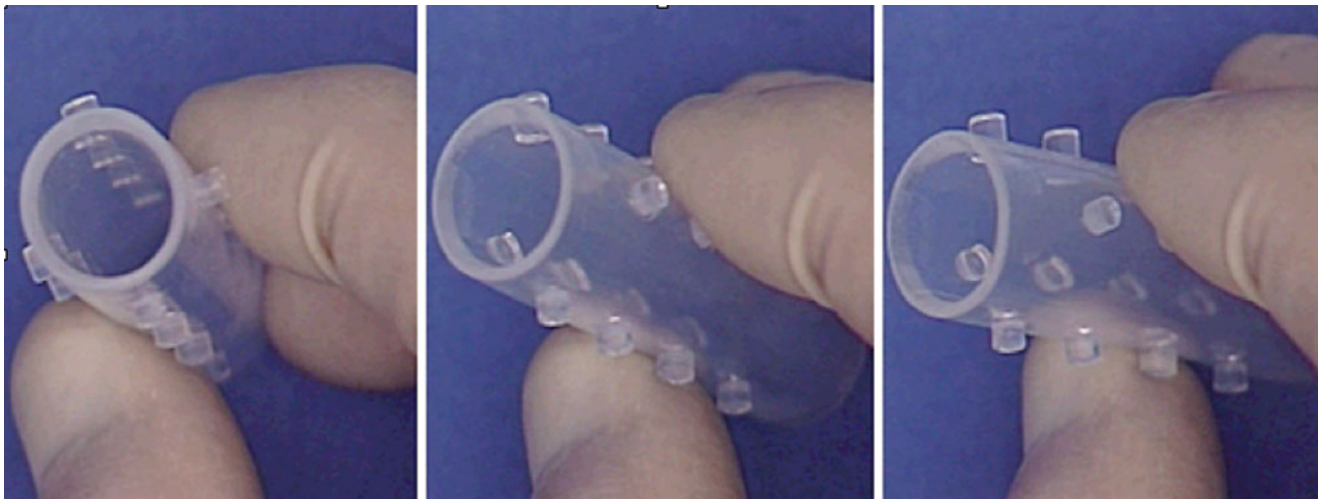

Fig. 29.1 The original Dumon stent (Tracheobronxane ®, Novatech, La Ciotat, France)

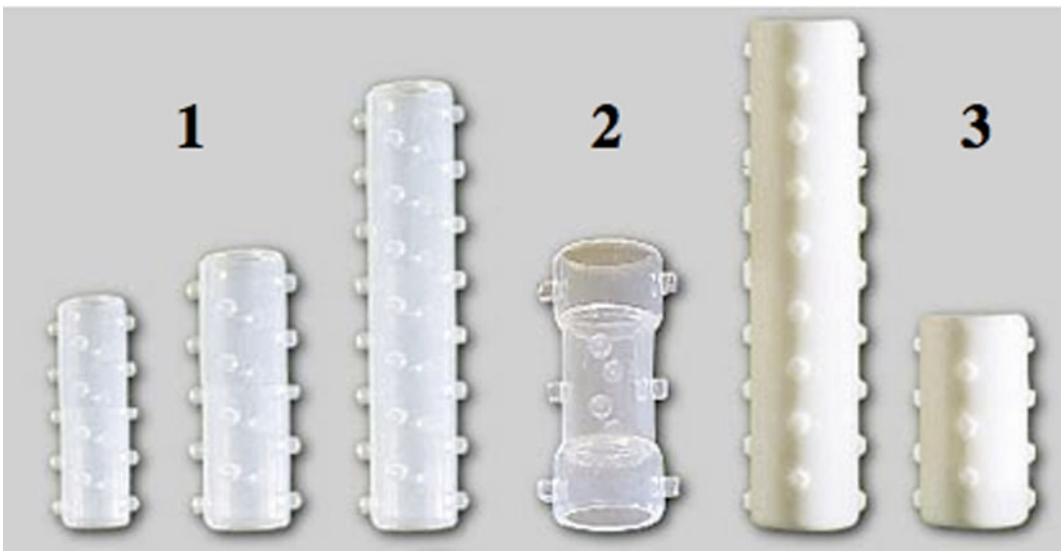

Fig. 29.2 The different designs of Dumon stent: (**a**) radiotransparent, (**b**) hourglass shaped and (**c**) radio-opaque

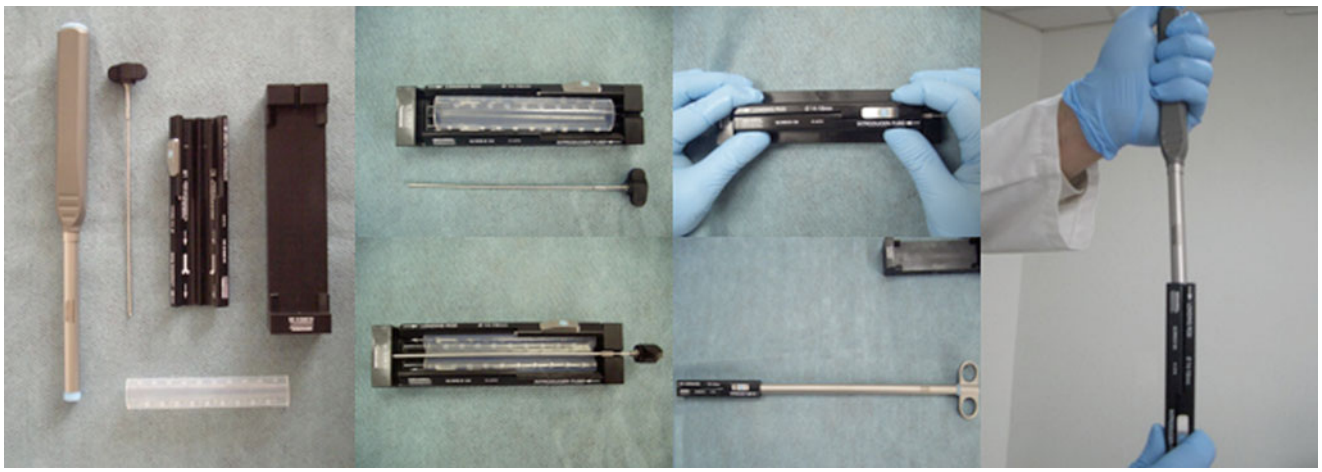

Fig. 29.3 Loading system for Dumon stent (Tonn-Applicator, Novatech, La Ciotat, France)

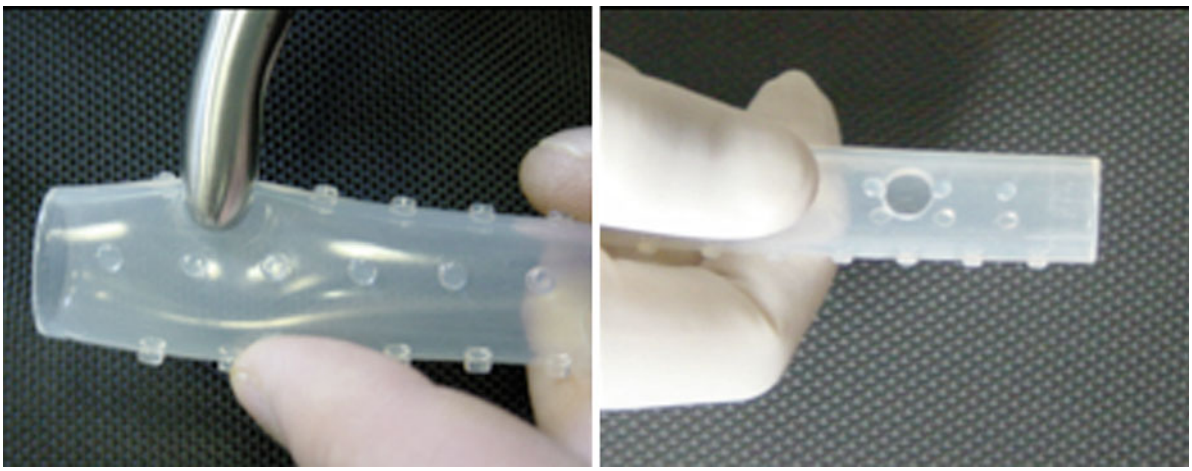

Fig. 29.4 On-site customization of a Dumon stent (dedicated forceps to create an orifice in order to ventilate a collateral bronchus)

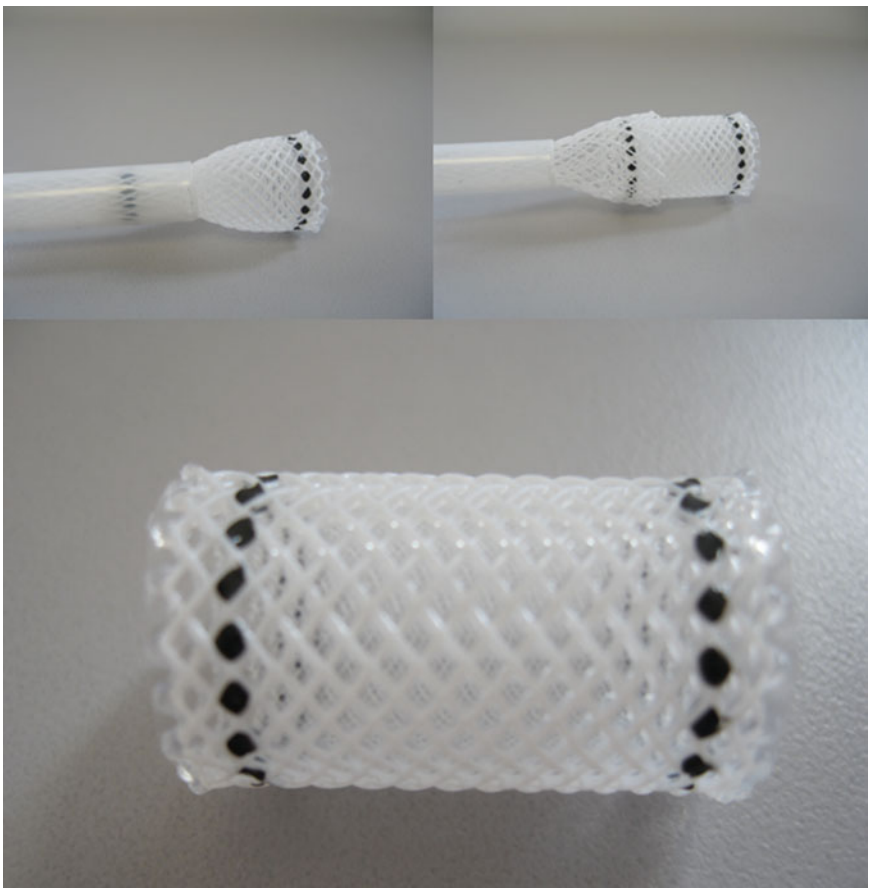

Fig. 29.5 Polyflex stent (Boston Scientific, Natick, MA, USA)

Polyflex Stent

The Polyflex stent (Boston Scientific, Natick, MA, USA) (Fig. 29.5) is made from polyethylene threads embedded in silicone. The walls of these stents are thinner than the walls of Dumon stents resulting in a better ratio of inner to outer diameter. The edges of these stents are sharper and the length of the stent changes depending on its compression state. Due to its design, a Polyflex stent can adapt slightly better to hourglass-type stenoses. The outer surface is slightly smoother, and the migration rate seems to be higher in comparison to the Dumon stent. Modified Polyflex stents with outer struts have been used successfully in recent studies. Little tungsten spots in the stent wall make them visible on

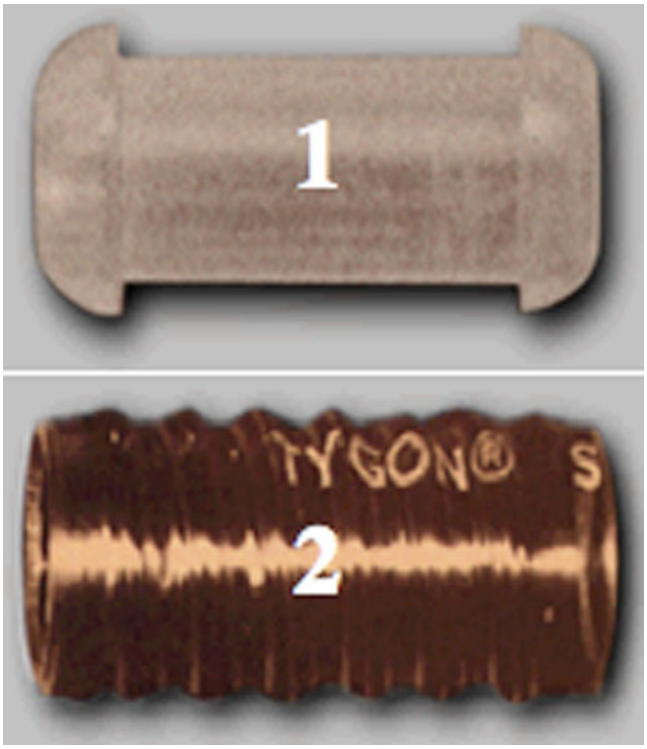

Fig. 29.6 Other silicone stents: (*1*) Hood stent (Hood Laboratories, Pembroke, MA, USA) and (*2*) Noppen stent (Reynders, Medical Supply, Lennik, Belgium)

chest radiographs. Polyflex stents are deployed out of a semi-rigid tube (Fig. 29.4). The skill and the training that is required to place them are comparable to the competence that is needed to insert Dumon stents.

Other Silicone Stents

Other CE-marked polymeric straight stents (Fig. 29.6) such as the Noppen stent (Reynders Medical Supply, Lennik, Belgium), which is made from Tygon, or Hood stents (Hood Laboratories, Pembroke, MA, USA), which are made from silicone, may be still available, but they are no longer advertised and have probably been replaced by the newly developed self-expanding metal stents.

As stated above, each stent has specific characteristics differing from those of the Dumon stent and therefore may provide a viable alternative depending on the indication.

Dumon silicone stents (Tracheobronxane®, Novatech, La Ciotat, France) are used nearly exclusively in our institution and are the most widely placed silicone stent, as such the remainder of the article will focus on this type of stent.

Indications

Any pathology leading a significant reduction in airway luminal diameter (greater than 50%) may be an indication for a silicone airway stent.

Five major indications have been established:

- Counteracting extrinsic compression from tumours or lymph nodes
- Stabilising airway patency after endoscopic removal of intraluminally growing cancer
- Treating benign strictures
- Stabilising collapsing airways (malacia and polychondritis)
- Sealing fistulas, e.g. stump dehiscences or fistulas between the trachea and oesophagus

Malignant Airway Stenosis

The most common indication is malignant airway obstruction from a bronchogenic malignancy. Malignant airway obstruction is often classified based on the airway involvement:

- Purely intrinsic involvement can often be managed with debulking techniques to remove the endoluminal tumour (Fig. 29.7). In this case, a stent may be placed as a bridge to the response to chemoradiotherapy, or alternatively it may be considered when there is a high risk of local recurrence**.**
- The vast majority of cases present with both tumour within the airway, intrinsic, and external compression of the airway, extrinsic. Treatment of mixed disease is usually multimodality with debulking and stent insertion.
- Extrinsic compression without intraluminal disease is readily treated with dilatation followed by stenting (Fig. 29.8)**.**

Other malignant indications for endobronchial stenting include endobronchial metastases from sites (e.g. oesophageal, thyroid, renal cell carcinoma, colon and melanoma) or alternatively low grade tumours (e.g. cylindromas, carcinoids).

Benign Airway Stenosis

Silicone stents are also useful as treatment for benign conditions resulting in central airway obstruction. The most common benign conditions leading to airway obstruction are

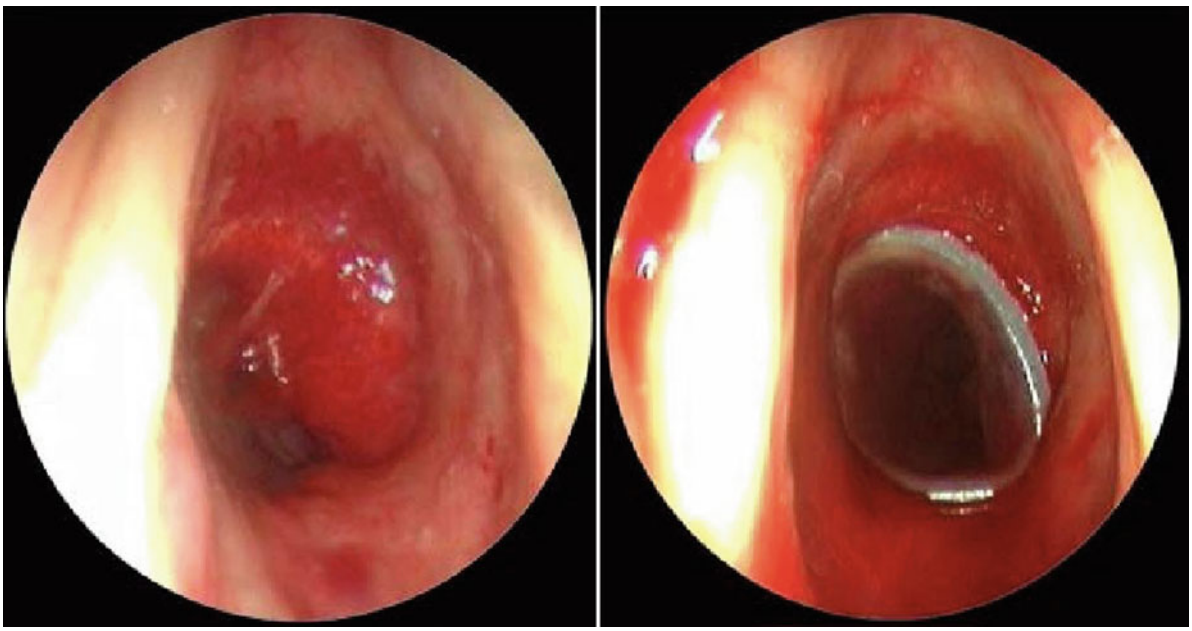

Fig. 29.7 Malignant obstruction of the trachea before and after placement of a silicone stent

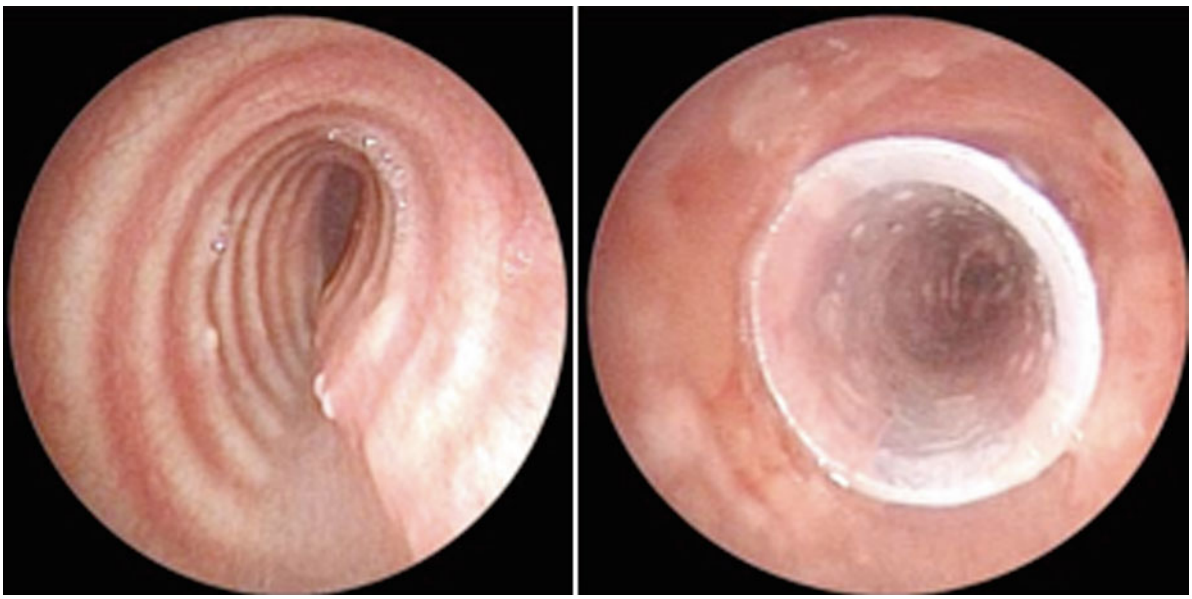

Fig. 29.8 External compression of the trachea before and after silicone stent placement

post-intubation or post-tracheostomy stenosis, post-anastomosis stenoses following sleeve resection, bronchial re-implantation, lung transplantation and tracheobronchomalacia.

Post-intubation or Post-tracheostomy Tracheal Stenoses (PITTS)

PITTS are classified between simple (web-like) and complex (involving the deterioration of the cartilaginous rings) (Fig. 29.9). Simple PITTS are generally not amenable to stent insertion unlike the complex PITTS which recur in about 70% after dilatation alone. Dumon stents are suitable for this indication as they are removable and do not jeopardise a possible postponed surgery unlike metallic stents. This prompted the FDA to published recommendations for the use of metallic stents in this indication.

Migration is probably the most challenging complication in this indication; its rate ranges from 11% to 17.5%, especially when the stenosis is very close to the vocal

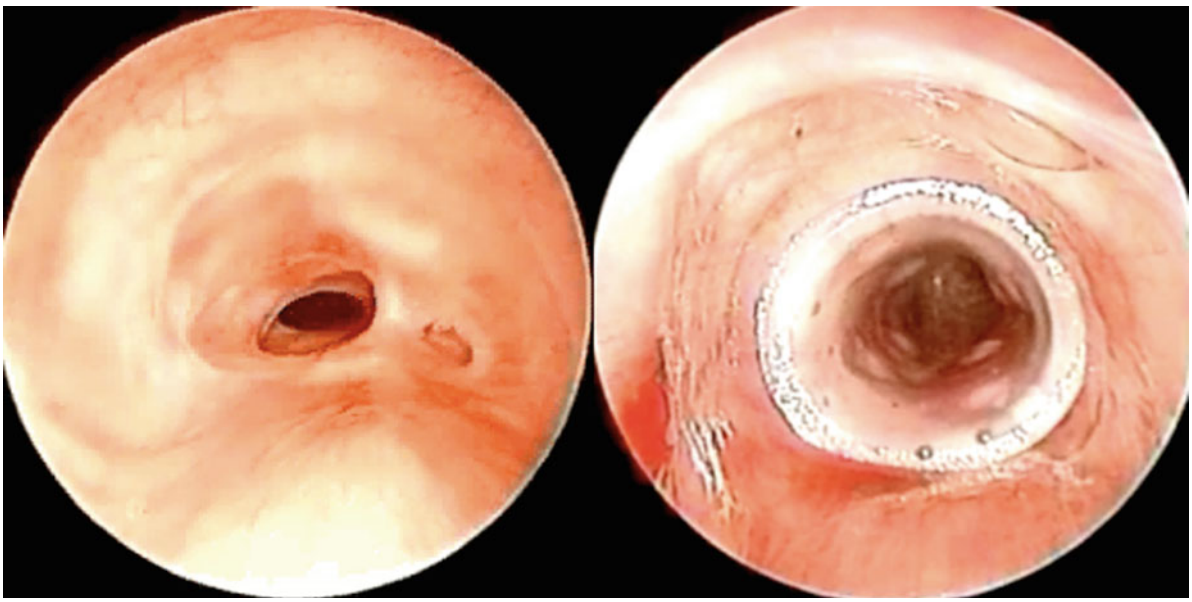

Fig. 29.9 Complex tracheal stenosis before and after silicone stent placement

cords. This can be reduced by the use of a dedicated hourglass silicone stent or by external fixation. Long-term results (no recurrence after stent removal at 1 year) vary from 40% (Brichet) when the stent is placed for 6 months to more than 60% when the stent remains in place for 18 months.

Bronchial Stenosis Following Lung Transplantation

Stent placement could potentially deteriorate mucosal ischaemia, and restenosis is a common finding. While the overall results (survival and clinical outcome) favour stent placement, a high rate of stent-related problems such as scarring, mucus plugging, bacterial colonisation and migration have to be accepted with currently available stents. It is advisable to select a stent that can be removed if necessary without causing further tissue damage. Recently, our group has published a retrospective study on Dumon stent placement in anastomotic stenosis after lung transplantation. The stents have been removed definitely in 70% of the patients without further recurrence.

Tracheobronchomalacia

During recent years, various stents have been used for these indications, but several unanticipated problems have been encountered. Therefore, most endoscopists have become reluctant about the use of permanent stent placement for malacias. The choke region can be identified with new techniques but any procedure may simply shift the choke region towards the periphery and there are no clear predictors whether a patient will benefit from a stabilising procedure. Therefore, in a trial and error approach, it can be considered to temporarily place a stent and test whether the patient improves clinically from this internal splinting. If they do, they are sent to the surgeon for external stenting techniques. If not, the stent is removed and physiotherapy and CPAP is recommended. The straight Dumon stent cannot be recommended for malacic stenoses as it is held in place by contact pressure between the airway wall and the studs. In flexible dyskinetic tracheas and gradually opening benign stenoses, it is prone to migration.

Airway Fistulas

Tracheo-oesophageal or Broncho-oesophageal Fistulas

Tracheo-oesophageal or broncho-oesophageal fistulas are most often secondary to malignancy. Oesophageal carcinomas show airway infiltration in up to 30% of cases. Fewer than half of these patients are resectable. If an oesophago-airway fistula develops, a rapid decline of the overall condition with distressing cough and aspiration pneumonia is usually observed. In rare cases, primary bronchogenic carcinomas invade the oesophagus causing similar problems. Insertion of an oesophageal tube improves the quality of life but usually fails to seal the fistula. Furthermore, the oesophageal tube can protrude into the lumen of the airway and compromise ventilation. Placement of an airway stent can prevent obstruction from the oesophageal tube and can help in sealing the fistula (Fig. 29.10).

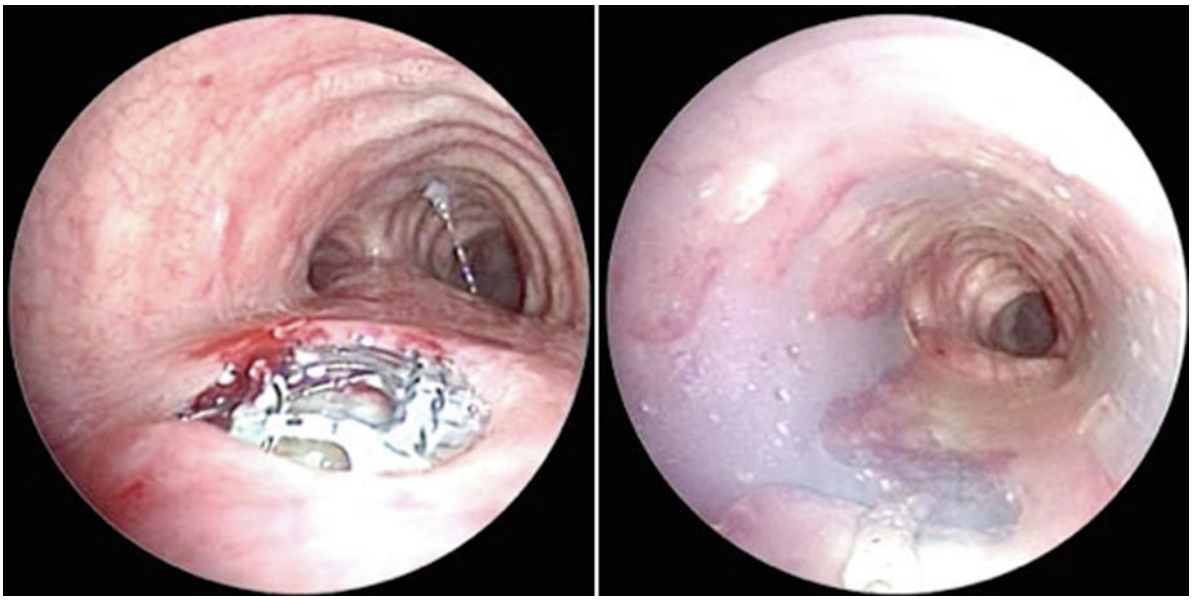

Fig. 29.10 Tracheo-oesophageal fistula before and after silicone stent placement

Broncho-pleural Fistulas

Post pneumonectomy or lobectomy stump fistula is a severe complication of thoracic surgery. Its incidence ranges from 4.5% to 20%. The incidence is lower for benign conditions compared to patients with a known malignancy. Surgery is the treatment of choice of this condition but endoscopic techniques have been advocated as an option when surgery is not possible or has to be postponed. Among them, placement of silicone stents is an option. Watanabe et al. reported successful sealing of a post-lobectomy fistula using a Dumon silicone stent, but long-term outcome was not described. Similar results were obtained in two clinical reports using Dumon silicone stents.

Contraindication

In life-threatening situations there are hardly any contraindications. However, other techniques should be used first before a stent is placed. Intraluminally growing tumours should be removed first by laser resection, for example, and then a larger stent should be placed if it is still necessary. Treating benign lesions requires particular caution as a stent might be harmful in the long run, even if the patient has an early benefit. In general, only removable stents should be used for these indications until a multidisciplinary team has determined inoperability. Instability of the airways is not a contraindication but hardly ever a good indication for permanent stent placement.

Silicone Stent Deployment

In our opinion, the deployment of a silicone stent must be performed using rigid bronchoscopy under general anaesthesia. In addition to stent deployment, the rigid bronchoscope serves as a useful tool both for mechanical tumour debulking and airway dilation prior to stent insertion (Fig. 29.11). Rigid bronchoscopy is essential for the insertion of Dumon stents as they are not auto-expandable.

The appropriate length of the stent is determined intraoperatively by using either the rigid optic or a flexible bronchoscope to measure the length of the lesion to be covered (Fig. 29.12). Preoperatively preliminary measurements can be estimated from the CT images and then confirmed endoscopically. Ideally, the stent should extend 5 mm above and below the abnormality.

With respect to the selection of the most appropriate stent diameter, this is based on the largest diameter rigid bronchoscope barrel utilised to maximally mechanically dilate the airway (Fig. 29.12). Stent diameter is decided upon on a case-by-case basis; however, some general guidelines will follow. In stenotic lesions of the trachea, 14–16-mm stents are often selected. The 12- to 13-mm and 10- to 11-mm stents are usually appropriate for stenoses involving the mainstem bronchi and bronchus intermedius, respectively. The sizing for fistulas and tracheobronchomalacia differs as there is no lesion to which the stent may anchor; therefore, in order to avoid migration, it is important to oversize the stent slightly.

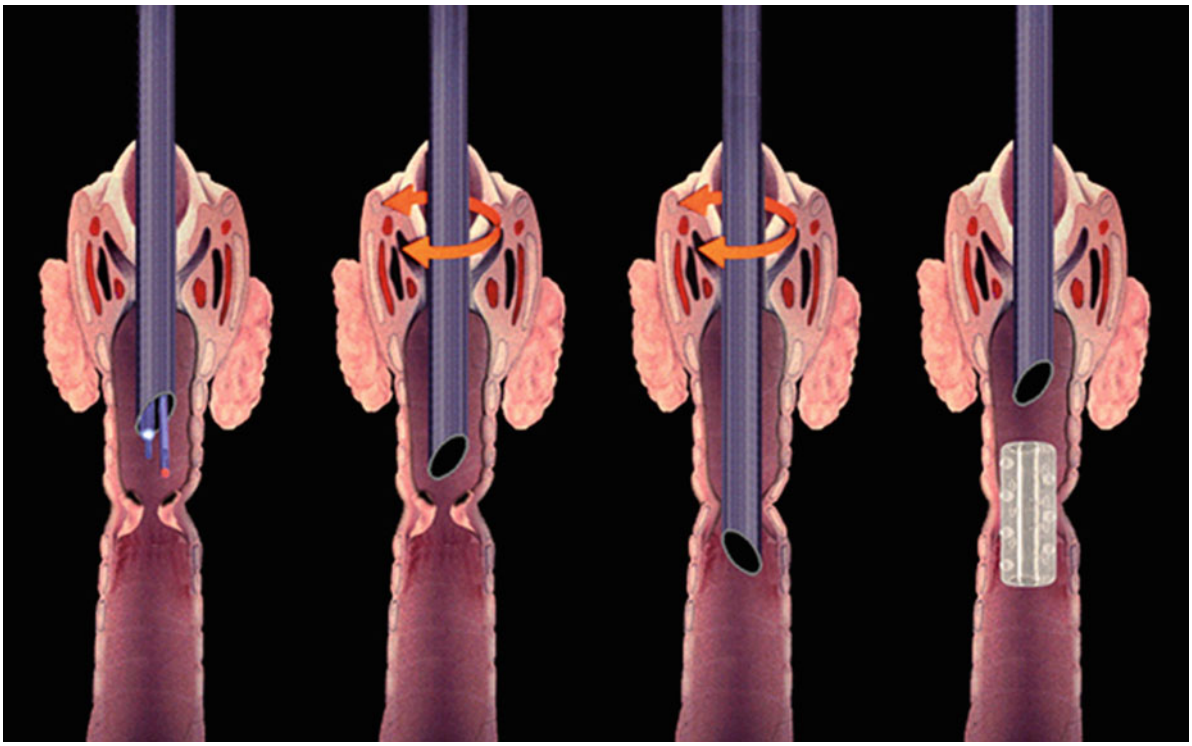

Fig. 29.11 Mechanical dilation using a rigid bronchoscope before stent insertion

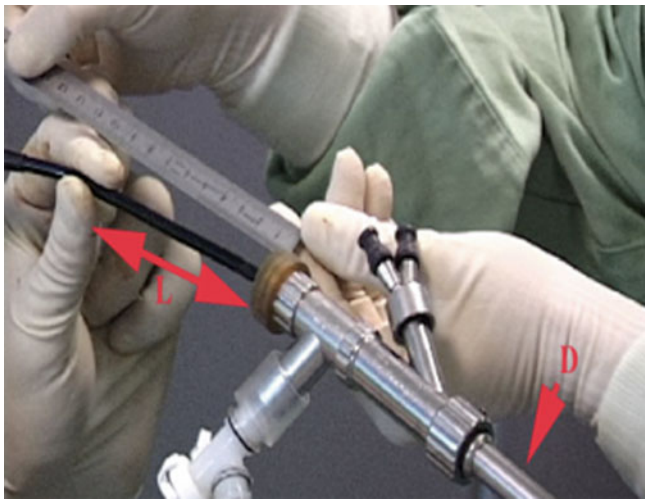

Fig. 29.12 Technique of length and diameter measurements

The stent is loaded into the dedicated stent deployment device and then positioned just distal to the lesion. The stent is subsequently moved more proximally into an ideal position with the rigid bronchoscopy forceps (Fig. 29.13). Pushing the stent more distally is rarely advised due to the risk of perforation at the level of the pathologic airway.

Upon deployment, the stent may not completely open, and a balloon catheter or one of the rigid instruments (rigid scope itself or the forceps) may be used to complete the expansion of the stent (Fig. 29.13).

No matter the indication for the airway stent, we recommend annual reassessment and replacement of the stent until such a time the stent is no longer indicated.

Stent removal is generally easy (Fig. 29.14). Using a rigid bronchoscope, rigid dedicated forceps are inserted alongside the optic. The proximal edge of the stent is grabbed and the stent is turned 360 ° on its position. Then the stent is pulled proximally, and its first 2 or 3 mm is inserted in the bevel of the rigid bronchoscope. This way, when the rigid bronchoscope and the stent will be pulled back in one block, the proximal edge of the stent will not damage the larynx and the vocal cords. The stent should not be pulled back on the entire length of the rigid bronchoscope. In some cases, when a silicone stent has remained in place for more than 2 years, its structure modifies and, during its removal, it can break in pieces of different sizes. All the pieces have to be removed one by one.

Complications

The major complications related to silicone stents include migration (9.5%), formation of granuloma (7.9%), obstruction secondary to secretions (3.6%) and bacterial overgrowth.

Migration is most frequently the result of under-sizing the stent diameter or alternatively due to tumour involution secondary to treatment. This complication is rarely fatal and most often presents clinically as cough or dyspnea. It is managed

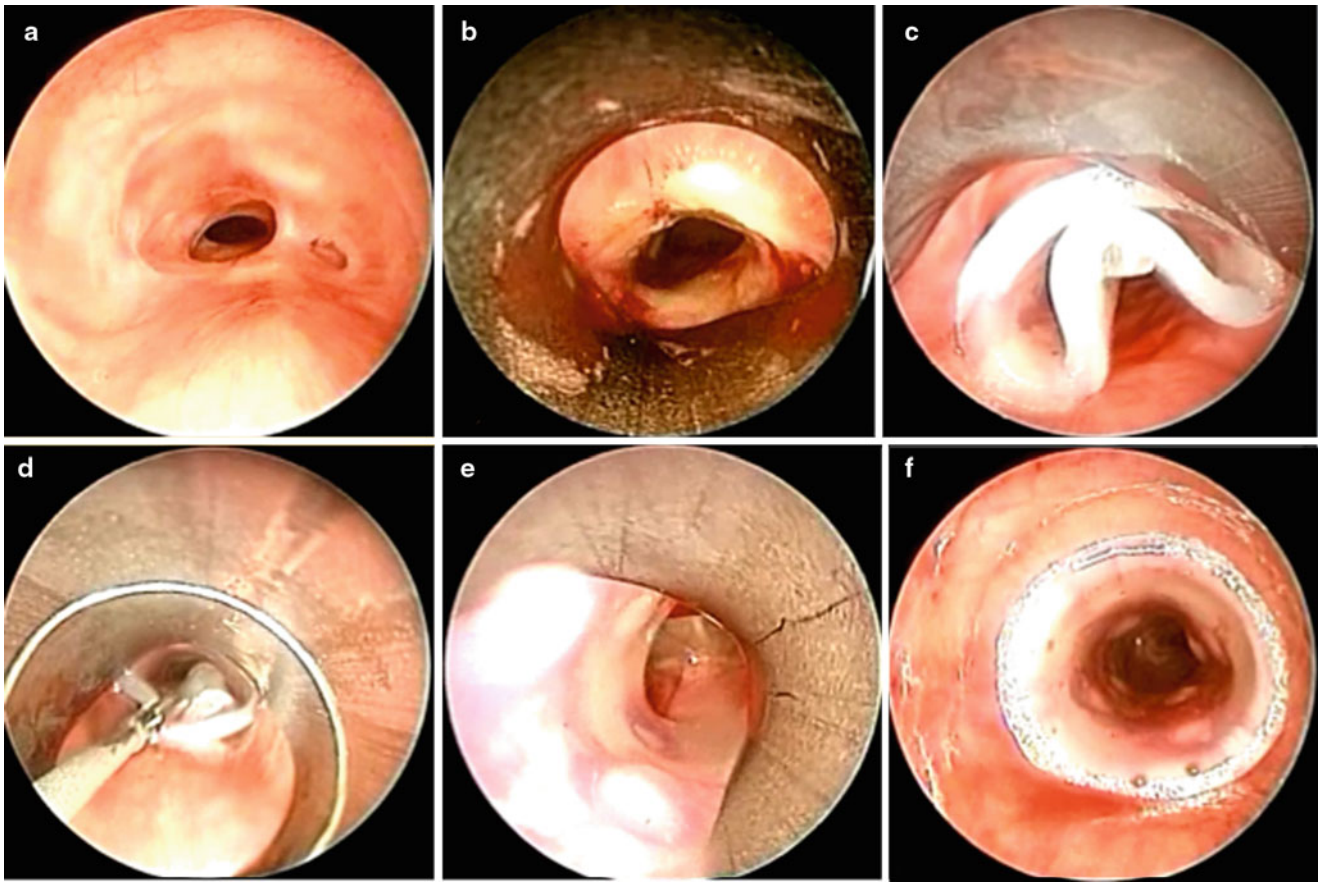

Fig. 29.13 Technique of silicone stent placement: (**a**) Tracheal stenosis. (**b**) Preliminary dilation using a rigid bronchoscope. (**c**) The stent is inserted at the level of the stenosis. (**d**) Rigid forceps unfold the proximal edge of the stent. (**e**) The rigid tube unfolds the body of the stent. (**f**) Final result after complete opening

simply by extraction of the migrated stent under rigid bronchoscopy and eventual replacement with a more appropriate sized stent. Percutaneous external fixation has been proposed to reduce the risk of migration.

Granulation tissue has a tendency to form at the proximal and distal margins of the stent and is related to chronic inflammation. They can lead to obstruction of the stent, and therefore, mechanical or thermal (laser, cautery, cryotherapy) means should be considered. Replacement of the stent may also be necessary.

Mucoid impaction of the stent leading to obstruction may be quite serious and even lethal. The risk may be reduced by maintaining humidification of the stent via nebulisation of sterile normal saline 2–3 times daily while the stent is in place.

Stents that become impacted with secretions most often associated with bacterial overgrowth should generally be removed and replaced.

Discussion

Advantages

Silicone stents are indicated for the vast majority of clinical indications whether malignant or benign, in contrast to metal stents that should for the most part be avoided in benign disease. Metal stents that are completely covered with silicone may be exception.

Although complications do occur with these stents, they are very rarely fatal and usually readily reversible. In point of fact, silicone stent removal is quite easy. They have a radial force sufficient to render them quite effective in extrinsic airway compression. In addition, they can readily be manipulated and moved within the airway without concern.

Techniques do exist to preserve ventilation to lobes that may be covered by an endobronchial stent, most commonly the right upper lobe with Y stents. These include fenestrations or addition of stents to the distal limbs, Borgne Y.

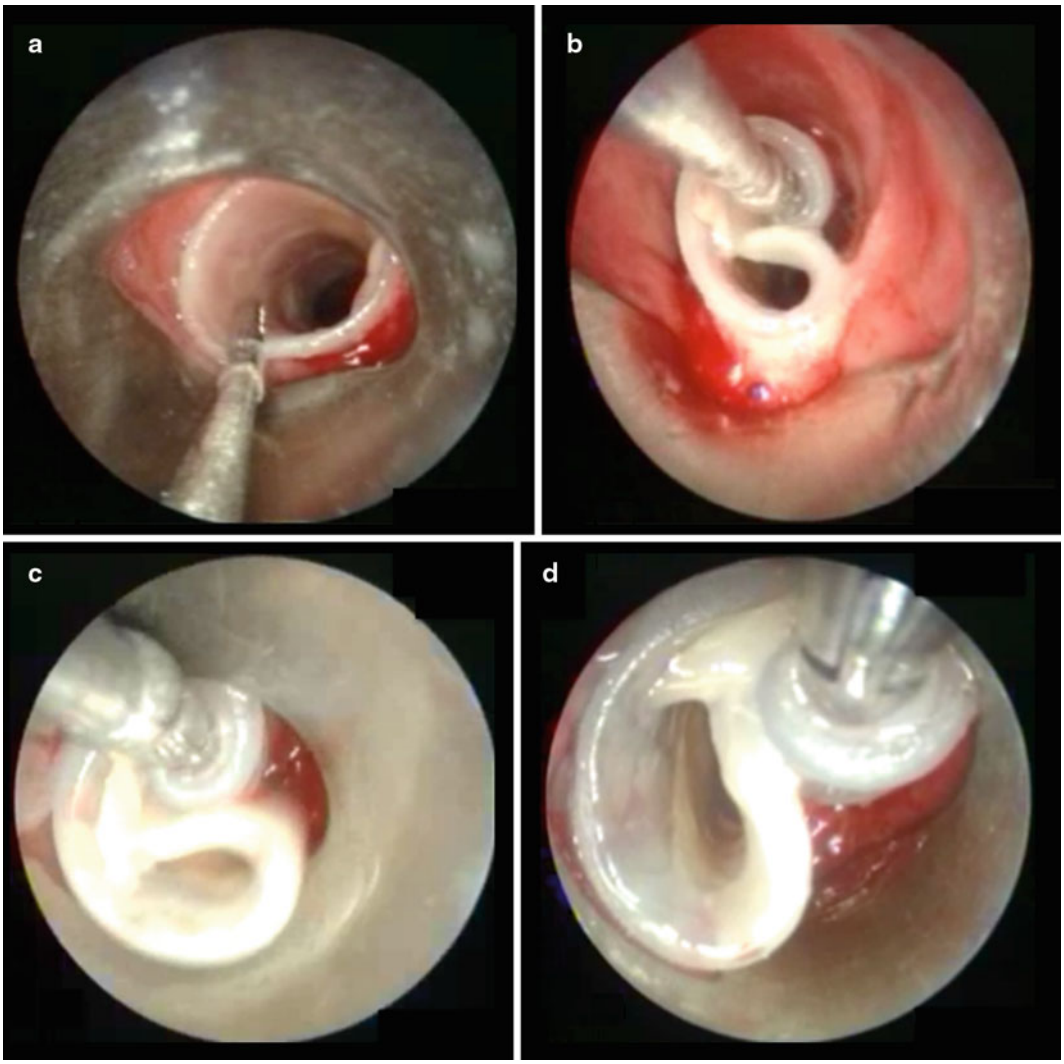

Fig. 29.14 Technique of stent removal (**a**) The rigid forceps grabs the proximal edge of the stent. (**b**) The stent is turned 360 ° on its position. (**c**) The first millimetres of the stent is introduced in the rigid tube. (**d**) The rigid tube and the stent are removed in one block

It is important to note that the cost of a silicone stent is significantly less than a metal auto-expandable stent in the order of 1.5–2 times.

Disadvantages

The necessity for rigid bronchoscopy and general anaesthesia for the placement of a silicone stent is considered by some as a disadvantage; however, in our opinion, this is not the case. These same skills/resources are essential for the management of potential complications that may result from the insertion of metal stents.

Due to pliability properties of the silicone stent, curvilinear conformations are not the ideal indication for silicone stents. In these situations, the stent may either involute centrally resulting in obstruction or even migrate due to the tendency to maintain its straight tubular conformation.

Conditions such as tracheobronchomalacia where there is a variable dimension of the airway may not always be ideally served by a silicone stent with a fixed diameter. Unfortunately, few other viable options exist for these conditions as metal stents, particularly those that are not fully covered with silicone are considered at least relatively contraindicated due to the difficulty with removal and high risk of fracture.

The tubular structure with the external studs of the Dumon stent may limit its ability to attain a complete seal between the stent and the airway wall. This may be important in the case of fistulas as there is potential for a small residual leak around the stent.

Finally, due to the greater thickness of the silicone stent compared to its metal counterpart, there is consequently a reduction in flow rate.

Conclusion

The ideal airway stent, that without complication and with physical properties rendering it ideal in all clinical situations, has yet to be developed. In the absence of the ideal stent, it is our opinion that the Dumon stent® has proven its efficacy in nearly all indications for endobronchial stenting. Complications with this type of stent are infrequent and rarely life-threatening. More importantly, the potential complications are readily manageable which is not necessarily the case with their metal counterparts (17, 18). The ease of removal renders them the best available option for benign disease and also in malignancy when there is an expectation of tumour response to chemoradiotherapy. In most centres, budgetary constraints must also be considered, and from this standpoint, silicone is by far superior to the much more costly option of a metal stent. Overall, it is our opinion that these airway stents are a safe, cost-effective and valuable tool in the management of all causes of airway obstruction and fistula.

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Y-Stenting Techniques

30

Daniela Gompelmann

Airway stents had been already implanted in the last century especially for the treatment of airway strictures, but the name "stent" has still a longer history. In 1856, the English dentist Charles Stent (1807–1885) and both his sons Charles R. Stent (1845–1901) and Arthurs H. O. Stent (1859–1900) created a thermoplastic material to cast dental models. In the years to come, this compound was trademarked under the name "stents". Today, the name "stent" is used for materials that are used to hold tissue in place or for a tube that is inserted into the lumen of any anatomical tubular structures to keep a previously blocked passageway open.

Indication for Y-Stent Placement

In general, tracheobronchial stents are implanted to reestablish patency of extraluminal compressed airways as well as to stabilize airway patency after endoscopic removal of endoluminal obstruction resulting from various benign and malignant processes. Malignant tracheobronchial stenoses that are commonly caused by adjacent lung cancer, esophageal carcinoma, thyroid carcinoma, or metastases of extrathoracic carcinomas are the leading indication for airway stenting. Benign stenoses often result from scarred tissue due to injuries to the mucosa with impairment of tracheal wall blood flow. The most common type of benign airway stenosis is the postintubation stenosis. But also posttuberculosis scar, anatomic strictures, or goiter can cause benign airway obstruction. Stenting of benign stenoses should only be considered if the patient is inoperable, because surgery is still the gold standard for treatment of benign stenoses.

In case of main carinal obstruction involving the distal trachea and the proximal main bronchi, the use of straight stents is limited due to the Y-shaped anatomy of the carina. Therefore, Y-shaped stents consisting of the tracheal body and two bronchial limbs are necessary to treat airway obstructions involving the lower trachea, main carina, and proximal mainstem bronchi.

Another indication for Y-stents is sealing fistulas and dehiscences between distal trachea and proximal main bronchi to the esophagus or to the pleural cavity that can be congenital or acquired as in majority of the cases. The most common cause for fistulas is malignant disease like esophageal carcinoma. Implantation of an esophageal tube often fails to seal the fistula; furthermore, a protrusion of this tube into the lumen of the airway with consequently compromising ventilation is often observed. The insertion of an airway stent prevents the protrusion of the esophageal tube and maintains ventilation. Furthermore, the airway stent helps sealing fistula.

Central airway obstruction involving the main carina can also result from tracheobronchomalacia – a kind of benign stenosis. Two types can be distinguished: cartilaginous and membranous tracheobronchomalacia. Cartilaginous tracheobronchomalacia reflects a loss of the structure of trachea or mainstem bronchi due to destruction of the cartilaginous rings. Membranous tracheobronchomalacia, also known as excessive dynamic airway collapse, is manifested by collapse during exhalation because of a laxity of the Pars membranacea. Patients, especially with cartilaginous tracheobronchomalacia, may benefit from the implantation of airway stents, but in this indication, several problems have been encountered, so that a permanent stent placement is mostly not recommended.

Contraindications

The placement of a Y-shaped airway stent is often performed in patients with life-threatening main carinal stenoses; therefore, there are no absolute contraindications in these situations. But stenting is associated with several problems, so

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DOI 10.1007/978-1-4614-4292-9_30,

that other endobronchial techniques and tools should be taken into consideration. In most cases, a combination of different endobronchial techniques provides the most efficacious management of tracheobronchial stenoses.

In case of benign main carinal stenosis, surgery is still the gold standard. Stent placement can also provide immediate relief from symptoms, but the stent-related problems in the long run should be kept in mind.

Y-Stent

Y-shaped stents imitating the anatomy of the central airways provide treatment of tracheobronchial stenosis involving the lower trachea, main carina, and proximal mainstem bronchi. In some case reports, the use of Y-shaped stents for airway stenoses around the carina between the right upper lobe bronchus and the bronchus intermedius is also described, but this technique has to be reviewed in further studies.

Generally, the bifurcation stents can be divided in three groups, depending on the material: polymer stents, hybrid stents, and self-expandable metallic stents. The first manufactured Y-shaped stents were polymer stents.

Y-Shaped Polymer Stents

In 1972, Neville et al. developed the first Y-airway Dacron cuffed silastic device replacing trachea and main bronchi. Eight years later, the Westaby T-Y Tube, manufactured by silicone, was implanted successfully as first bifurcated prosthesis. The side limb of the Y-stent requires tracheotomy. Today, this prosthesis is only used for extremely long stenoses from the cricoid to the upper lobe bronchi. The later introduced bifurcated stents are held in place by their geometric shape and do not longer require a tracheotomy. The Orlowski Y-Stent, created from polyvinyl chloride with internal metal armor, provides treatment of extremely strictures. This stent cannot be compressed. The Hood Y-Stent, fabricated of flexible silicone, is softer than the other bifurcated stents than those listed above. This stent can be implanted in several techniques, but requires good skill in rigid bronchoscopy. The silicone Dumon Y-Stent is like the other straight Dumon Stents covered with little studs on the outside preventing migration and a non-adherent smooth inner surface reducing problems with incrusted secretions (Fig. 30.1a, b). In 2004, the clinical results of implantation of a Dumon Y-Stent in 86 patients suffering from central airway obstruction or fistula were published by Duteau et al. In 53.4%, the stenosis was due to intraluminal growing cancer and in 14% due to extrinsic compression. In 31.4% of the patients, a fistula was the indication for airway stenting. Main carinal

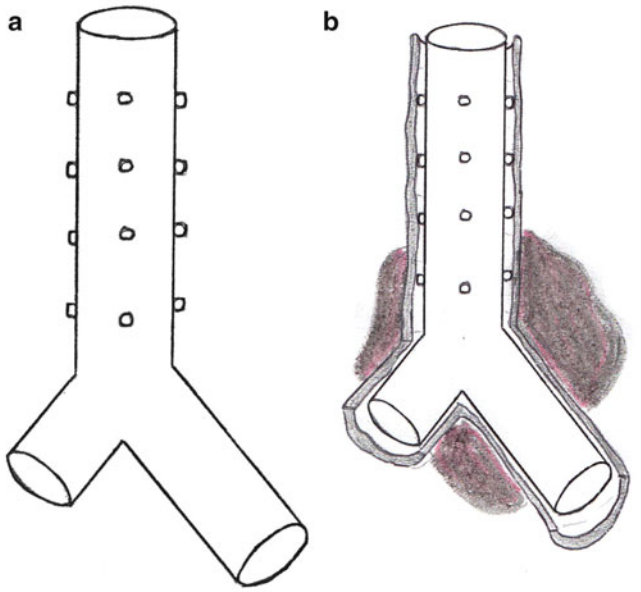

Fig. 30.1 (**a**) Dumon Y-Stent. (**b**) Dumon Y-Stent in the obstructed central airways

necrosis was observed in 1.2%. Subjective symptomatic relief following stent placement was evidenced in 84 patients. The Y-stents remained in place for an average of 133.6 days. One stent required immediate removal due to stent migration. After 3 months of follow-up, 44 patients continued to benefit from the stent. At 6 months, only 19 patients were living with stents in place.

Y-Shaped Hybrid Stents

The Dynamic Y-Stent is an anatomically shaped bifurcation stent with an anterolateral silicone wall reinforced with a metallic hoop and a non-reinforced posterior wall resembling the membranous part of the trachea (Figs. 30.2a, b, and 30.3). This flexible posterior membrane mimics the dynamic of the Pars membranacea of the trachea. During coughing, the membrane bulges inward, thereby increasing its efficacy. For sealing fistulas, the Dynamic Y-Stent should be chosen following the placement of an esophageal stent, because the non-reinforced posterior wall presses nicely against the anterior wall of the esophageal stent. Removal of this stent is possible without problems at any time. In 1994, Freitag et al. published the results of a 5-year experience of 135 patients suffering from compression stenoses, strictures, or malacias of the central airways or tracheoesophageal fistulas, who were treated with the dynamic bifurcation airway stent. A stent implantation could be achieved in all patients without any major complication and provided immediate relief of

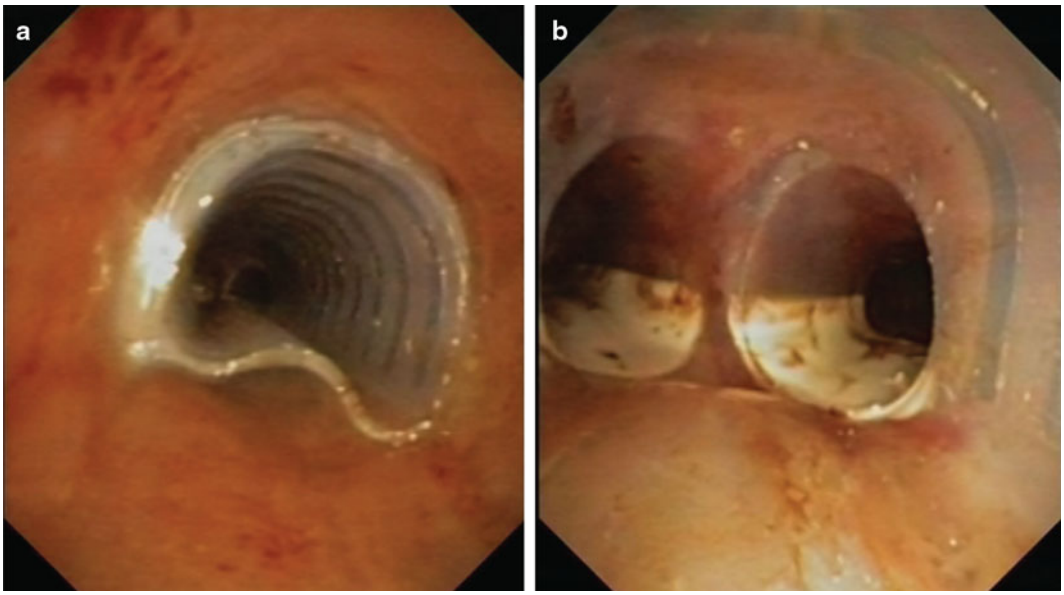

Fig. 30.2 (**a**) Dynamic Y-stent. Distal end (**b**) Dynamic Y-stent. Proximal stent

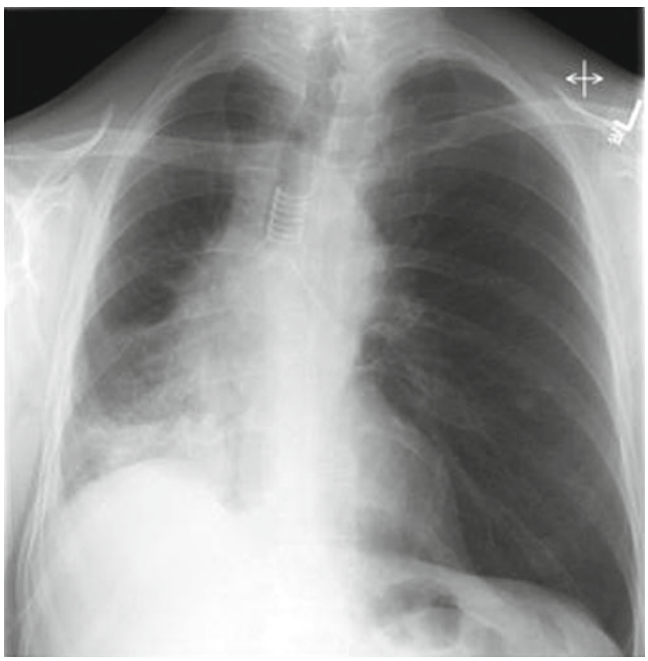

Fig. 30.3 Chest X-ray after implantation of a Dynamic Y-stent

dyspnea in most cases. Three months following stent implantation, 24 patients were still alive with stent in place. Twenty-seven times, a successfully tumor-specific treatment with subsequent reduction of central airway stenosis, surgery or further endoscopic treatment allowed removal of the stent. Only in 1 out of these patients, a second stent implantation was required. Eighty-five patients died with the stent still in place after a mean survival time of 123 days in most cases due to their malignant disease.

Y-Shaped Metallic Stents

The covered metallic Y-shaped (Fig. 30.4 and 30.5) stents are excellent for use in palliation of airway obstruction. They are easy to place and are characterized by an excellent conformity for irregular tracheal or bronchial walls. Furthermore, problems with retained secretion and mucostasis can be observed.

The bifurcated Nanjing stents also known as Y-Carina-Ecostent are woven metallic stents consisting of highly elastic nitinol wire. They are completely covered expect the distal 5 mm of the right branch. The stents are available in different lengths and diameters. These self-expanding stents are implanted using an introducer system under fluoroscopy. The stent placement is facilitated by radio-opaque markers at different points of the stent. The edges and inner surface are smooth, but problems like retained secretion has been observed. The disadvantage of the metallic stents is the difficult removal. In 2007, the first clinical results of the implantation of self-expandable metallic Y-stents were published by Yang et al. Five patients with a complex tracheobronchial stenosis due to lung cancer or esophageal cancer were successfully treated with these metallic stents. No procedure-related complications were observed. All patients had immediate relief of respiratory symptoms of dyspnea or cough. In another trial, published in 2008, 35 patients with complex tracheobronchial stenoses involving the carina were treated with a self-expandable metallic Y-stent. Stenosis was caused by lung cancer (n = 25) or esophageal carcinoma (n = 10). In all patients, the delivery of the integrated self-expandable Y-shaped metallic stent in the carinal area was

Fig. 30.4 Self-expandable metallic Y-stent

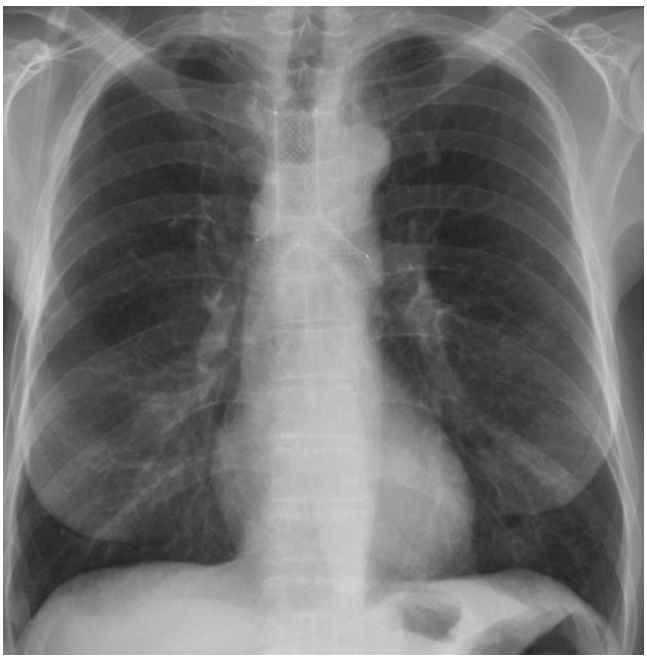

Fig. 30.5 Chest X-ray after implantation of a self-expandable metallic Y-stent

technically successful and well tolerated. All patients had immediate relief of respiratory symptoms. Clinical success was observed in 31 patients (89%) 1–7 days after stent placement, the procedure failed in four patients (11%).

Implantation Techniques

Stent implantation is commonly combined with other endoscopic procedures alleviating the acute airway obstruction. In case of intraluminal tumor growth, laser-assisted resection, electrocautery, or cryodebridement offers removal of neoplastic tissue prior to the stent implantation. In the event of extrabronchial compression, balloon dilatation or bouginage can be used to extend the airway followed by stent implantation for stabilization of the narrowed airways. Prior to the implantation of the stent, the length and diameter of the stent have to be determined. The length of stent should cover the stenosis in both main bronchi as well as in the trachea ≥ 5 mm. The diameter of the stent should greater than the diameter of the remaining stenosis after mechanically treatment or dilatation.

Although, stent implantation is possible using flexible bronchoscope, rigid bronchoscopy remains the preferred method for stent implantation that provides handling potential complications. There are different techniques, the Y-stent can be implanted depending of the type of Y-shaped stent. The most commonly utilized Y-stents are the Dumon Y-Stent, the Dynamic Y-Stent, and the self-expandable metallic Y-stents.

Dumon Y-Stent

The Dumon Y-Stents are the most frequently used stents worldwide. The bifurcated model is the latest development in the Dumon series. These stents are inserted ideally by using the introducer system of a special rigid bronchoscope (Efer, Harrell Universal Bronchoscope). This bronchoscope features a series of interchangeable tubes of various sizes. Two different implantation techniques can be distinguished. In the “pushing method”, the Y-stent is placed inside the tube of the bronchoscope and then pushed blindly out above the main carina in the trachea. Afterwards, the limbs of the Y-stent may have to be twisted and positioned with opened grasping forceps to the carina. In the “pulling method”, the Y-stent is deposited completely in the main bronchus that is most narrowed by the tumor. Afterwards, the stent is pulled back using rigid forceps until the shorter bronchial limb slips into the other main bronchus.

Dynamic Y-Stent

In 1994, Freitag et al. reported about a new insertion technique for the placement of bifurcated airway stents, especially of the Dynamic Y-Stents. These Dynamic Y-Stents can be inserted with special forceps – modified foreign-body-

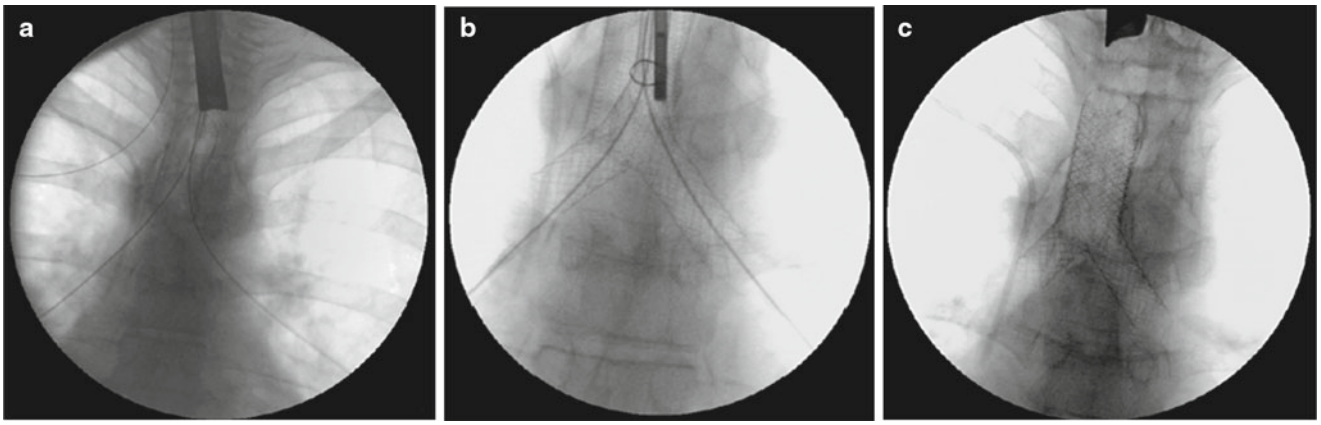

Fig. 30.6 Implantation of Y-Shaped Metallic Stent (**a**) The two guide wires are inserted into the both main bronchi. The delivery system is advanced over the two guide wires into the trachea. (**b**) The two branches of the Y-stent localized in the main bronchi are released by pulling back the threads. (**c**) Y-stent is totally released by withdrawing the introducer sheath

removal forceps with extra long jaws simplifying the passage of the stent through the vocal cords and the tracheobronchial stenosis. Prior to the implantation of the Y-stent, rigid bronchoscopy is performed to measure the length of tracheobronchial stenosis. Afterwards, the bronchoscope can be removed. The stent is grasped from inside with these dedicated forceps that are advanced to the carina under visual control using a normal laryngoscope. Then, the forceps are opened and the bronchial limbs glide into the main bronchi as the forceps saddle the carina. Afterwards, a movable pusher is used to anchor the stent while the grasping part of the stent forceps is withdrawn. After complete removal of the forceps, the patient is reintubated with a short bronchoscope or tracheoscope, and stent position and function are checked.

Y-Shaped Metallic Stents

The self-expandable metallic stents are implanted using a special delivery system with the preloaded stent. Usually, a rigid tracheoscope, a flexible bronchoscope, and two guide wires are required. The implantation should be performed under general anesthesia and HJ ventilation. This tracheobronchial stent is inserted under fluoroscopy. First, the two guide wires are advanced into both main bronchi, one in the left bronchus and one in the right bronchus. Afterward, the delivery system is inserted to the carina along the two guide wires. Under fluoroscopic guidance, first, the two branches of the Y-stent localized in the main bronchi can be delivered. Finally, the tracheal stent is deployed by withdrawing the introducer sheath, thus completely releasing the Y-stent. The stent position is then checked bronchoscopically. The technique used for placement of the self-expandable metallic Y-stent is shown in Fig. 30.6a–c.

Stent-Related Complications

Despite the benefit of the airway stents, there are some possible stent-related problems.

Mucostasis

One of the most commonly reported side effects is mucostasis due to missing of mucociliary clearance inside polymer stents and covered stents and due to the inability to cough efficiently (Fig. 30.7a, b). This complication is observed particularly in case of rigid stents or very long stents, dynamic stents cause fewer problems. Furthermore, colonization with bacteria and fungi of this mucus layer is a common event associated with halitosis and infection. In 1999, Noppen et al. performed protected brush specimen sampling of the airway in 14 patients prior to airway stenting and following the implantation of the airway stents. Within 3–4 weeks of stent implantation, airway colonization caused by potentially pathogenic microorganisms was found in 11 of these 14 patients. In no case, however, airway colonization was associated with clinical signs of infection. A 2009 published review including 23 articles regarding to stent treatment in 501 patients revealed that 19% of patients experienced stent-associated respiratory infection. Pneumonia was the most common type (47%), followed by bronchial infection (24%), cavitary pneumonia/lung abscess, and intraluminal fungus ball.

The best preventative measure to avoid mucostasis is regular inhalation with saline. Furthermore, anti-inflammatory topical drugs can be used and are probably more useful than mucolytics.

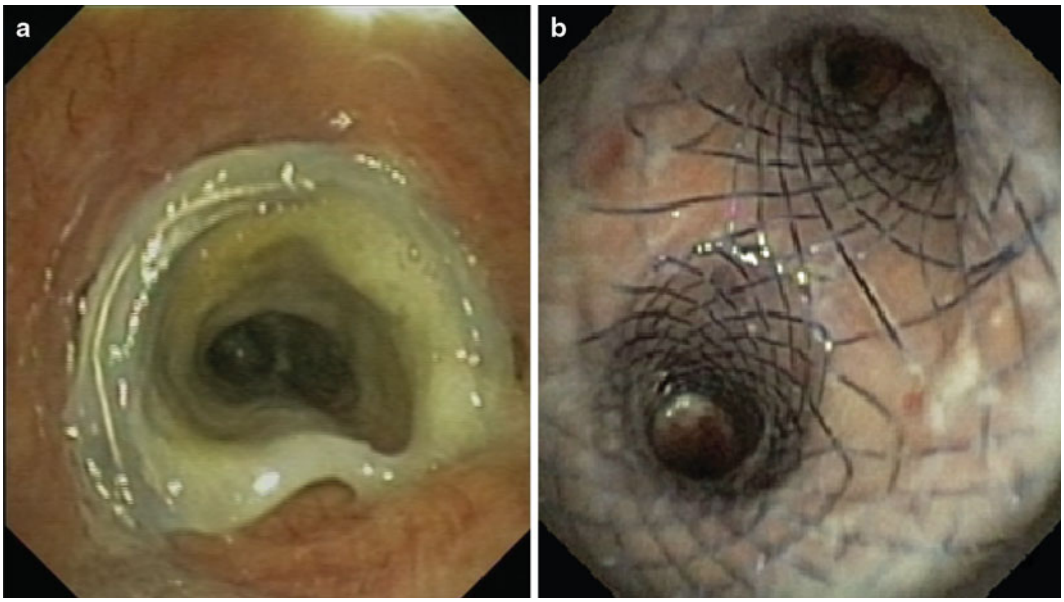

Fig. 30.7 (**a**) Secretion in a Dynamic Y-Stent. (**b**) Secretion in a self-expandable metallic Y-stent

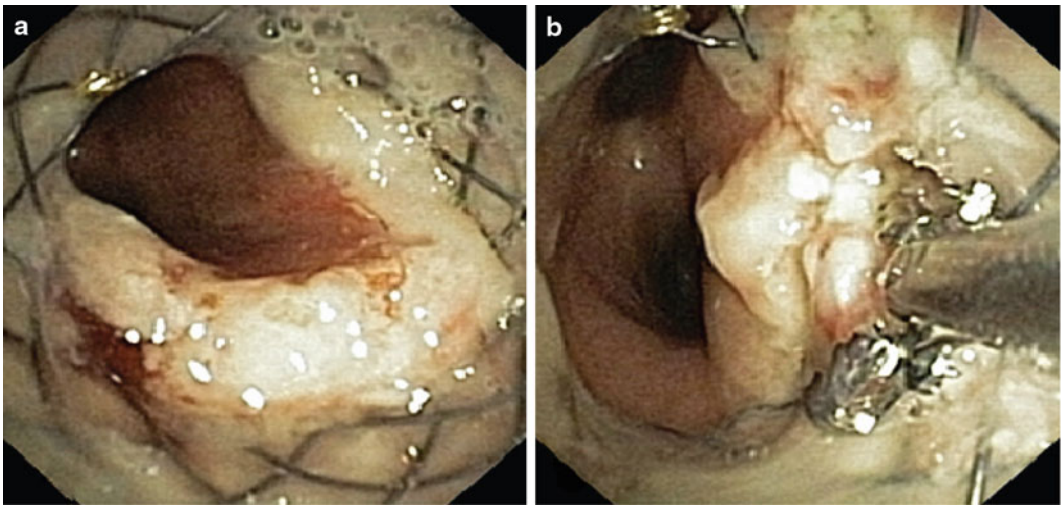

Fig. 30.8 (**a**) and (**b**) Granulation tissue formation in a self-expandable metallic Y-stent

Granulation Tissue Formation

Development of granulation tissue is due to the high localized pressure of the Y-stent on the mucosa (Fig. 30.8a, b). The reaction of normal non-neoplastic bronchial tissue on implanted non-covered metal airway stents has been studied in a prospective trial in 2005. First, the basal membrane was destroyed by stent filaments, the microvessels in the submucosa were eroded, and then a slow papillomatous growth of granulation tissue and a non-specific inflammatory reaction could be documented. In 22% of the 18 included patients, a polypoid tissue hyperproliferation led to clinical significant partial restenosis.

To reduce the tissue hyperproliferation, the airway stents should fit tight to avoid dynamic friction without a high pressure on the mucosa that would impair microcirculation. Besides, the end of the stents should be smooth to reduce the risk of development of scarring and shrinking at the stent edges that also could lead to restenosis. Granulation tissue formation is less frequently seen in immunocompromised patients. In 2008, the degree of in-stent granulation tissue formation was evaluated in 18 immunocompetent patients and in 11 patients receiving immunosuppression therapy. Tissue hyperproliferation was significantly lower in the immunocompromised patients. The immunosuppression therapy may

have an inhibitory effect on granulation tissue. However, general application of steroids cannot be recommended.

Another complication is the stent luminal narrowing due to stent invasion by adjacent neoplasm. In uncovered stents, the malignant tissue grows through the meshes and begins to obstruct the stent lumen. But also in case of polymer stents or covered metallic stent, the tumor can grow over the edges and can protrude into the stent. To avoid the last stated risk, it is important to select a stent with an appropriate length.

A restenosis due to occlusion by malignant tissue or granulation tissue formation requires recanalization mechanically or by cryotherapy or argon-beamer coagulation to restore airway patency. In addition, internal or external radiation therapy afterwards can prevent further development of granulation tissue.

Stent Fracture

Stent fracture is one of the major concerns especially in case of self-expandable metallic stents, because it can cause wall injuries promoting granulation tissue formation, bronchial wall perforation, and intraluminal obstruction. Dyspnea, infection, and cough are the clinical signs.

Stent Migration

Stent migration is nearly not observed in Y-stents, because they are hold in place by their geometric shape. In 4 out of 100 Dynamic Y-Stents, a cephalad migration could be detected. These complications were observed either after tumor response to treatment or after long-term bouginage effects.

Summary

Successful therapy of stenosis or fistula of the lower trachea, main carina, and proximal mainstem bronchi usually requires the use of a Y-shaped stent. Especially in case of malignant stenoses, these airway stents provide palliation. Benign airway stenoses are still an indication for surgical treatment, but for patients who are definitely inoperable, an airway stent is also an option. Generally, the bifurcation stents can be divided in three groups, depending on the material: polymer stents, hybrid stents, and self-expandable metallic stents. The most commonly utilized Y-stents are the Dumon Y-Stent, the Dynamic Y-Stent, and the self-expandable metallic Y-stents. The Y-stents provide immediate relief from dyspnea; however, they are also associated with several problems like mucostasis, granulation tissue formation, tumor overgrowth, and stent fractures. Therefore, it is important to select the patients prior to airway stenting who will truly benefit from stent implantation.

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Montgomery T-Tubes

31

Carla R. Lamb

Introduction

This chapter will review the T-tube device including its indications, contraindications, placement, and other management issues. The evolution of this device provides a bridge to the airway, specifically when tracheal disease of either benign or malignant nature creates significant airway compromise. This device can be both a bridge to definitive treatment or serve as the only treatment. It is important to understand optimal patient selection, sizing of the device, as well as technique of placement and removal.

History and Device Description

The first prototype for the Montgomery T-tube was introduced by Dr. William W. Montgomery in 1964, for use in the setting of cervical trachea reconstructive surgery. It was manufactured from rigid acrylic material in two separate pieces but found to be costly and difficult to manufacture and insert. The following year, the revised one piece T-tube was introduced which was manufactured from flexible silicone material. It was easier to insert with less mucosal irritation even with prolonged usage.

The vertical limb of the T-tube is placed in the tracheal lumen, while the horizontal limb protrudes out through the tracheostomy site. The design of the uncuffed tube allows minimal mucosal reaction by using silicone and tapered ends minimizing friction and interaction with the airway mucosa. Also, the junction of the T is widened by the curvature allowing decreased tissue reaction at the tracheostomy site. The curvature at the T junction also allows the suction catheter to be directed either superior or inferior by simple movement of the external limb to the opposite side. For instance, if the suction catheter is to be directed inferiorly, the external limb should be pushed superiorly prior to inserting the suction catheter.

Many modifications to the original device have been made since its introduction, but the fundamental structure and functionality remain unchanged (Figs. 31.1 and 31.2). There are now a wide variety of these devices which allow for a more custom fitting. Significant modifications include addition of ridges and grooves on the external limb of the tube to allow attachment of a ring washer and speaking valve. This also prevents accidental dislodgement of the external limb into the trachea during suctioning and to allow patients to speak with the T-tube, respectively. The external limb was made longer to accommodate obese patients. The thoracic T-tube has an extra long distal vertical limb to allow treatment of thoracic stenosis that may be more distal. Other important modifications include a Montgomery T-tube fused with a Y stent forming a T-Y stent, which provides airway support to the entire airway from the tracheostomy site to the bilateral main stem airways.

The T-tube size ranges from the pediatric 6.0 mm diameter to 16 mm accommodating different airway sizes in both small children and adults. It minimizes the risk of migration which is especially important given its proximity to the vocal cords. In cases of stenosis or surgical resection of high tracheal disease, the proximal portion of the T-tube can be placed above the vocal cords. The wide variety of options provides either a clear or radiopaque T-tube. For the patient who has a proximal subglottic stenosis, the proximal T-tube limb is tapered to accommodate this while providing a more viable airway. The length of the individual arms allow for patient specific customization. Measurements can be provided to the manufacturer and a custom tube can be made very efficiently. However, the physician is also free to customize the standard tube onsite at the time of the procedure. It is very important when shortening the limbs the intraluminal ends must be smoothed and beveled to reduce formation of granulation tissue. This can be done by cutting the

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DOI 10.1007/978-1-4614-4292-9_31,

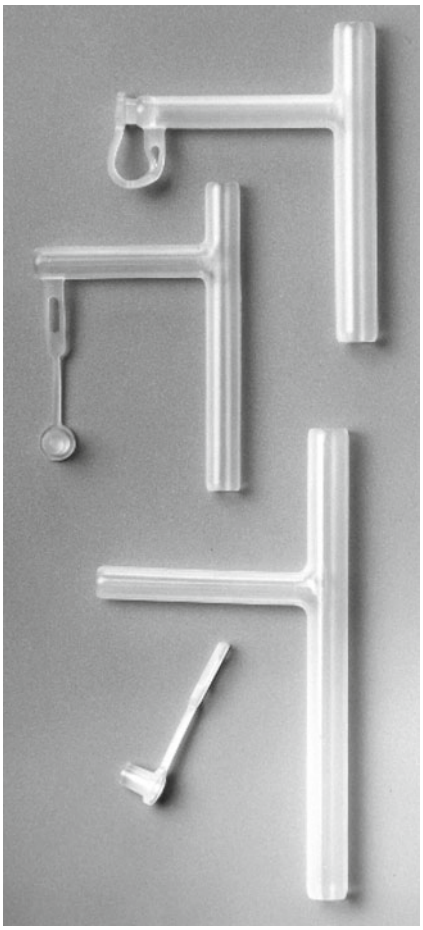

Fig. 31.1 T-tube (Printed with permission from Hood Laboratory)

tube with a scalpel blade and smoothing the edges with sandpaper. There is a customizing kit that can be ordered by the manufacturer. To properly size both the diameter and length of the T-tube, CT scan imaging of the trachea with virtual images, 3D reconstruction, coronal, axial, and sagittal views are very helpful. Bronchoscopic visualization pre-procedure is also helpful to assist with measurement confirmation. It is important to be mindful if the proximal disease permits, to avoid allowing the proximal vertical limb to be at or < 5 mm from the true vocal cords. It is also important to assure that the internal airway limbs of the stent cover the pathologic site and that all limbs fully open upon placement. If there is notable persistent infolding of any of the limbs after placement, then this likely indicates that the stent diameter is too large and must be replaced with a smaller diameter tube. Ideally, the fit would be flush to the mucosa limiting any sliding movement of the tube against the dynamic tracheal walls.

Indications

Initially developed for use in the setting of providing support for a reconstructed trachea and tracheal resection and anastomosis, and acute tracheal injury, the indication has expanded to cover other etiologies of upper airway obstruction requiring structural support. The indication can be divided based on the etiology of airway disease: neoplastic and nonneoplastic.

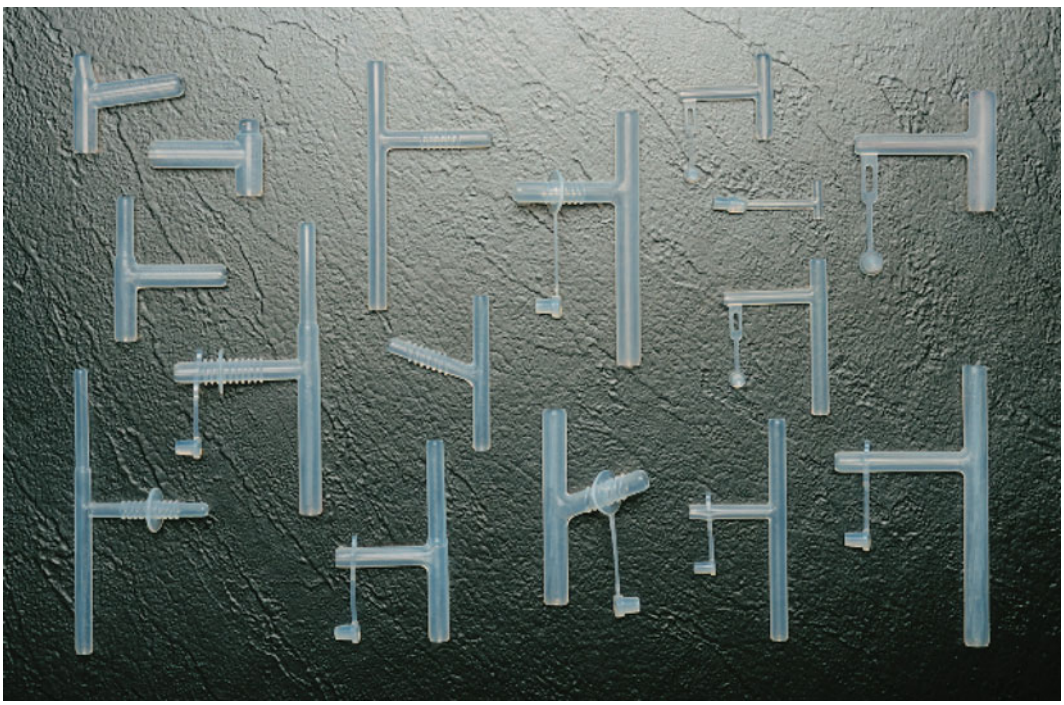

Fig. 31.2 Variation of T-tubes (Printed with permission from Hood Laboratory)

Neoplastic Etiology

This category includes airway obstruction secondary to either primary tracheal tumors or metastatic diseases of the airway. Metastatic cancers that can involve the trachea such as the esophagus, as well as those mediastinal tumors that may result in extrinsic airway compression such as thyroid or lymphoma, may create comprise to airway function.

Nonneoplastic Etiology

This category of disease includes postanastomotic stricture and postintubation stenosis. Less common reasons include stenosis associated with tuberculosis, amyloidosis, sarcoidosis, and postradiation stricture. Aneurysms of the vascular structure surrounding the airway or congenital abnormalities can cause extrinsic compression and airway obstruction. It must be noted that surgical correction of nonneoplastic tracheal stenosis is the gold standard, and stents such as the T-tube should be used in surgically uncorrectable cases either due to prohibitive patient surgical risk factors and technical difficulties or as a bridge to definitive surgical correction. However, there have been many cases where the T-tube has been left in place for prolonged periods of time up to 16 years without any significant complications or patient intolerance. A T-tube due to its anchored placement may be more optimal than a standard cylindrical silicone tracheal stent based on disease that may be more proximal in the trachea with the possibility of tracheal stent migration to the vocal cords. In those patients who require more frequent pulmonary toilet with a suboptimal cough, the T-tube provides a much needed access into the airway for suctioning that would not be possible with a tracheal stent alone. A T-tube may be more comfortable and more cosmetically appealing to patients.

In respect to the surgical management of tracheal disease, the T-tube can be used as an adjunct to surgical management:

1. Temporary airway support prior to definitive surgical resection.
2. Compliment high tracheal and subglottic resection postsurgery: the T-tube is placed at the time of the surgery and left in place for prolonged period, allowing appropriate airway remodeling and preventing postsurgical stenosis.
3. Failed primary tracheal resection: in patients who develop restenosis postsurgically or partial separation of anastomosis can benefit from prolonged T-tube use.
4. Primary definite therapy with T-tube if surgically unfeasible: the T-tube can be placed either indefinitely or for a prolonged period to allow airway remodeling.

Contraindications

In patients likely to require prolonged positive pressure ventilation in the immediate future, the T-tube would not be the recommended option due to the proximal air leak from the proximal tracheal limb of T-tube. This will be discussed further in detail below. Placement of a Montgomery T-tube must be cautiously considered in patients with significant thick respiratory secretions due to a higher incidence of possible stent occlusion from mucus impaction. One case series showed a 9.3% complication rate secondary to secretion retention, requiring intervention such as bronchoscopy. Caution should always be used when the tube inner diameters are small, as seen in children due to the risk of airway obstruction from dried secretions. Meticulous care in sizing, position, and cleaning is required.

In cases of the proximal vertical limb of the T-tube extending above the vocal cords preventing full glottis closure, there is an increased risk of aspiration. Patients who already have a clear history of aspiration should not undergo T-tube placement.

Insertion and Removal

The presence of a tracheostomy opening is a mandatory prerequisite for placement of the T-tube. The original insertion method described by Dr. Montgomery with some modifications is as follows: the airway is secured with a rigid tracheoscopy tube with jet ventilation applied via a working side channel of the tracheoscope, and then using a hemostat, grasp the inferior limb of the vertical tube after folding it upon itself. This is inserted through the tracheostomy opening inferiorly. The hemostat is released and then used to grab the proximal vertical limb next inserting it superiorly. The external limb is pulled gently to allow the other limbs to open up and be directed appropriately (Fig. 31.3).

There have been many new approaches and modifications to the original method described. One popular method suggested by Cooper et al. in 1981 involves using the rigid bronchoscope and an umbilical tape threaded through the horizontal limb, proximal limb of the T-tube, then through the tracheostomy opening and exit through the rigid bronchoscope at the vocal cords. By inserting the inferior limb then pulling on the umbilical cord, this allows quick insertion and alignment of the T-tube. Subsequently, many authors published variations of this method using the umbilical tape and either the rigid bronchoscope or endotracheal tube.

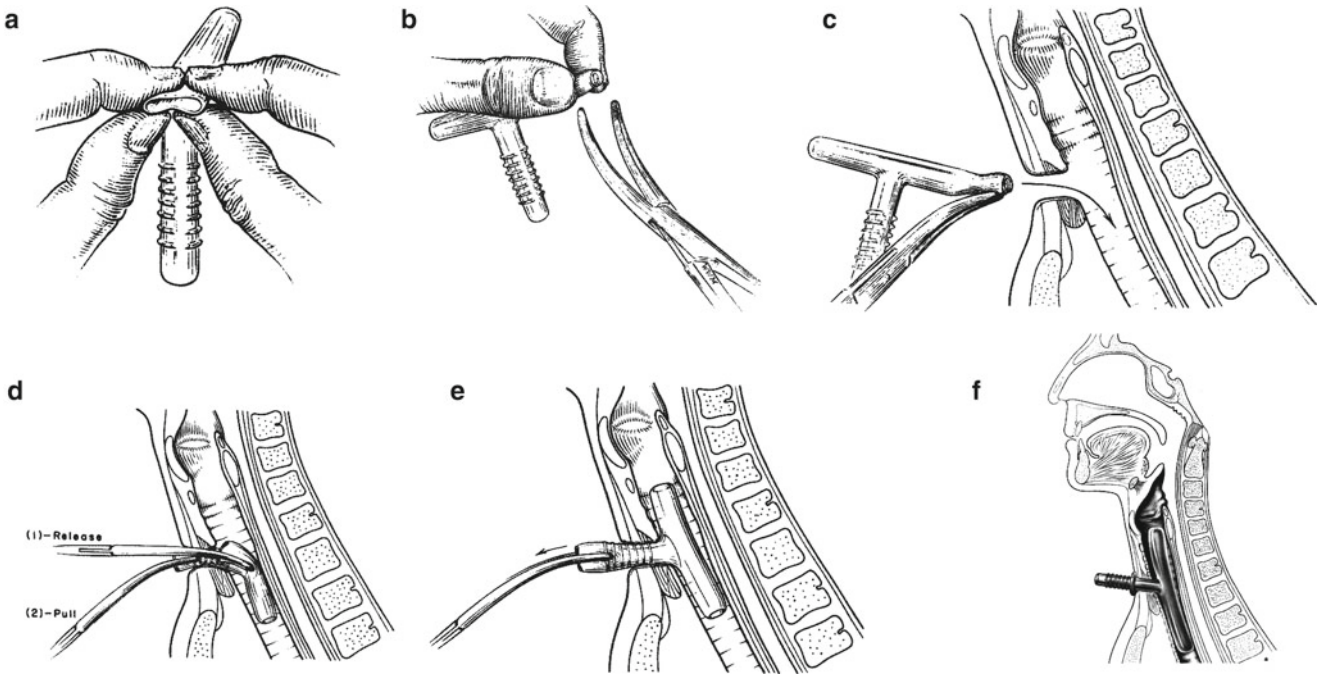

Fig. 31.3 Demonstration of one method of placing a T-tube (Printed with permission from Boston Medical)

Other interesting methods suggested by some authors involve loading the T-tube onto the endotracheal tube prior to insertion. A size 6.0 mm endotracheal tube in the adult can either be inserted through the horizontal limb into the distal vertical limb or the proximal vertical limb of the T-tube then inserted into the trachea and exited inserted into the trachea and exited out through the tracheostomy site, then pulled back into the tracheostomy site.

The removal of the T-tube is usually done under general anesthesia and is simpler than the insertion. A generous amount of lubricant with or without lidocaine applied to the external tracheal site is helpful. The horizontal limb is pulled away from the trachea with a gentle traction until the T-tube is dislodged from the airway. In emergency, the removal can be performed while the patient is awake. The bronchoscopic exam postremoval is necessary to assess the stability of the airway postremoval. The unstable airway must be addressed immediately postremoval for safety. It is always important to have a difficult airway intubation tray, a percutaneous dilational tracheostomy tray, a tracheostomy surgical tray, and a variety of sizes of tracheostomy tubes at the bedside.

Data Review

The available data on the efficacy of T-tube come mainly from retrospective review of case series and case reports. Due to the nature of the medical problems being treated with the T-tube, as well as the relatively low prevalence rate, there has been no randomized clinical trial comparing the T-tube to other alternative methods of airway management.

Two of the largest published retrospective review series describe 140 and 75 patients, respectively.

These patients received a T, TY, or a modified extended T-tube. Eighty-six patients had a benign etiology due to postintubation stenosis. The majority of patients demonstrated that the T-tube was effective in providing a long-term airway. Only 12 patients required the T-tube more than 5 years. The longest reported use of the T-tube in a patient was 16 years. The 20% of patients who failed to respond to the T-tube were due to airway edema or granulation tissue, requiring removal within the 2 months of insertion. The overall serious complication rates were low. One death due to tracheal hemorrhage was directly attributed to the T-tube occurring at 5 months postinsertion.

Another published series described 75 patients with complex benign lesions requiring the T-tube. The majority of the patients had postintubation stenosis (76%). Over half of the patients had contraindications to surgery with the T-tube being the only treatment. Complications occurred in 27 patients with 20 requiring some intervention in the form of ablation for granulation tissue, bronchoscopic cleaning, and temporary replacement with a tracheostomy tube cannula. The T-tube failure rate reported was very low. No death related to the T-tube was reported. In most published series, in approximately half of the patients, the T-tubes were able to be removed successfully in those patients who either underwent definitive surgery or their primary disease was

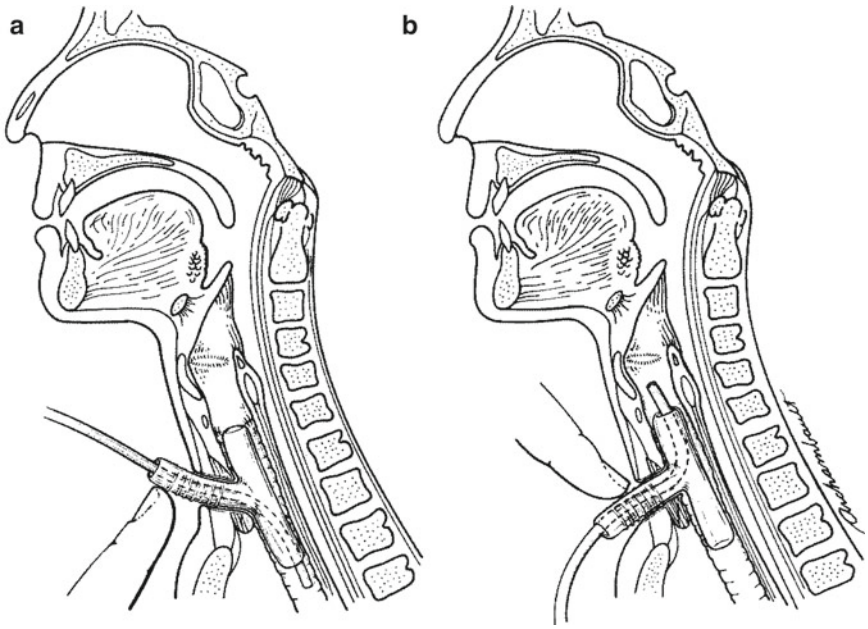

Fig. 31.4 Demonstration of technique for suctioning with T-tube in place (Printed with permission from Boston Medical)

successfully treated. In those whom surgery was contraindicated, the successful removal rate decreased approximately to one fourth.

Maintenance

The T-tube must be cared for meticulously in order to prevent occlusion with inspissated mucus. A high level of care is needed immediately postinsertion and for the subsequent 7 days, including plugging the external limb to prevent dry air and allowing the patient to speak. Frequent suctioning with hypertonic saline or acetylcysteine nebulization appears to assist with clearance of secretions. The use of a physiotherapy valve described as a flutter valve for pulmonary toilet is also helpful. The frequency of nebulization and suctioning can be decreased after the first week based on the patients individual needs. By positioning the horizontal limb of the T-tube, a suction catheter can be directed either superiorly (Fig. 31.4a) or inferiorly (Fig. 31.4b).

Anesthesia

During the earlier stages of placing T-tubes, there was the problem with anesthesia due to concerns of both air and volatile anesthetic gas leakage through the upper limb of the T-tube during insertion. Dr. Montgomery recommended in his original paper to simply place a Shiley arterial embolectomy catheter from tracheostomy site/horizontal limb of the T-tube into the upper vertical limb to obstruct the lumen. This leads to a closed circuit between the anesthetic equipment and lower respiratory airways. Now that total intravenous anesthesia (TIVA) is the standard, this does not pose the same concern.

There are methods advocated by other authors, which include insertion of an laryngeal mask airway (LMA) and either providing ventilation through the LMA and proximal vertical tracheal limb portion of the T-tube. When using the LMA to ventilate, the external limb must be occluded and vice versa.

Hebeler T-tube is a T-tube with an internal balloon in the proximal limb of the tracheal stent that can be inflated to create a closed circuit for ventilation.

In case of an airway emergency case, the 6.0-mm endotracheal tube can be passed through the tracheal stent portion of the T-tube to establish the airway. The internal/external diameters of both the T-tube and the endotracheal tube must be used in selecting the appropriate size to have readily available prior to the procedure.

Additional Considerations

There have been a number of novel approaches to providing anesthesia and positive pressure ventilation in the patient that may already have a preexisting T-tube. This can be unfamiliar territory to most emergency room physicians, intensivists, anesthesiologists, and general pulmonologists when a patient presents either with acute respiratory failure or for an elective

procedure requiring general anesthesia. It is always advisable to consult otolaryngology and interventional pulmonary medicine for acute management. In the decision to ultimately remove the T-tube and either replace it with a cuffed endotracheal tube or a cuffed tracheostomy tube directly into the pre-existing tracheostomy tube site, it is imperative to stabilize and maintain the airway while expertise and equipment are being brought to the bedside. It should be noted that the T-tube provides additional challenges due to the nonstandard fitting at the external opening of the horizontal limb to the usual anesthesia/ventilator circuit. A tracheal tube connector measuring 15 mm is required. Depending on the nature of the proximal tracheal disease in the patient with a T-tube in situ, another alternative would be to perform an awake intubation with bronchoscopic visualization.

One-way speaking valves can also be provided to the patient and be attached to the extraluminal portion of the T-tube to prevent misplacement.

Summary

The T-tube is a unique and effective device in the management of variety of proximal airway diseases providing a dual function of tracheostomy tube and tracheal stent. It is well tolerated by patients without significant serious complications, although its use in younger patients must be done with extra caution. Because of its unique features, it will continue to be an important part of therapeutic options in airway management. Knowledge of this device is important not only for those placing the T-tube but also for any clinician caring for patients with airway diseases.

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Electrosurgery

32

Tom Gani Sutedja

Equipment and Technical Background

Electrocautery (EC) or diathermy is the use of an electrical probe to conduct electrical current for heating target tissue in contact with or in close proximity to the probe. A high-frequency electrical generator is standard equipment in most hospitals, and high-frequency alternating electrical current is needed to avoid neural and muscular response. The system can be plugged in easily in any electrical socket, and many probes are readily available for an easy hook up. Electrical current can be conducted safely by the insulated metal wire probe toward the target tissue, and due to the voltage difference between the probe and tissue, electron current density generates heat at the point of contact as tissue resistance for electrons is high, resulting in coagulation or fulguration.

Argon plasma coagulation (APC) uses ionized argon plasma gas for conducting electrons to spray large tissue surfaces in a noncontact fashion, resulting in superficial homogeneous coagulative necrosis. The argon plasma stream easily conducts electrons around the corner to follow the many angulations of the segmental bronchial tree branches. APC is popular in gastrointestinal and trauma surgery for obtaining quick tissue fulguration over large surface area to create a homogeneous tissue necrotic crust of several millimeters in depth.

Various EC and APC applicators are available for the clinical practice: contact monopolar probe, bipolar probe, electric snare or loop, electric knife, and forward- and side-firing APC probes.

Every practitioner can choose any particular EC or APC method that can better suit each treatment purpose, based on personal skill and preference. Switching between the different methods and probes in a treatment session can be easily done.

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Flux density of electrons is an important principle as the probe functions as a focusing point for electrons. The ultimate coagulative necrosis depends on voltage difference between probe and tissue, i.e., wattage setting; the surface area of contact, e.g., smaller probe has a smaller surface area of contact and much higher electron flux at the point of impact causing more intense heat generation; and the total duration of energy application. Mucus, blood, and any metal part within the target volume with better electric conductance may, however, cause electron leak that will reduce local heat formation.

In practice, the effect of tissue coagulation and fulguration is immediately visible for the bronchoscopist as tissue becomes white colored or charred. These changes match with the histological damage seen on the bronchial wall under microscopy. This is in practice important as visible effect provides an immediate visual feedback to the bronchoscopist. Tactile feedback by palpation using monopolar probe while coagulating is the advantage of the contact mode.

The familiarity of operators in using electric appliances should be taken into account. The wider availability of various easy interchangeable rigid and flexible applicators for EC and APC is of great practical advantage to easily perform coagulation or fulgurate tissue followed by mechanical debulking in quickly restoring airway passage. EC, APC, and cryotherapy (see separate chapters) can be used more comfortably as the equipments' setup is easy for use in an outpatient treatment setting of a bronchoscopy unit or in ICU care.

General Treatment Strategy

The use of EC contact mode, i.e., by palpation to coagulate or hot biopsy forceps for hemorrhagic tumor, has a similar handling as Nd:YAG laser using the sapphire probe for contact coagulation. The noncontact APC method is comparable to CO_2 laser for quickly obtaining superficial necrotic layer (see Fig. 32.1). The use of EC and APC and its reusable applicators is technically comparable to the noncontact firing of

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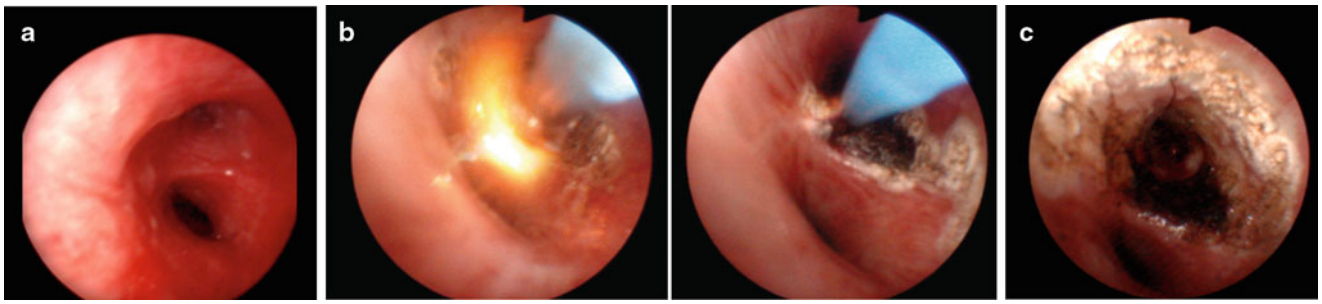

Fig. 32.1 A patient with GOLD III COPD, diabetes, and previous history of CABG and poor vascular condition used aspirin and was presented with hemorrhagic sputum. Superficial spreading squamous carcinoma reconfirmed by a panel of pathologists. Lesion extent was established under autofluorescence bronchoscopy extensive sampling of mucosal biopsies. (**a**) High-resolution CT scan with 1-mm slice thickness and FDG-PET scan did not show any abnormality; thus, this extensively spreading intraluminal lesion is classified as CT/PET occult. Locally, he was treated with argon plasma coagulation (**b**), and the necrotic crust can be seen immediately after APC treatment (**c**). He remains disease-free after 5 years follow-up. Recently, squamous cancer recurrence was diagnosed in the orifice of the superior part left upper lobe bronchus, and due to invisibility of distal tumor extension, external radiation treatment with respiratory gating has been commenced. There is a slight thickening on the HRCT scan seen, and locally FDG-PET scan shows local avidity

Nd:YAG and other lasers. Laser fibers are much more expensive, goggles and coverage of mirroring surfaces for protecting personnel from potential eye damage are necessary. Laser beam goes straight and cannot be flexibly angled around the corner in contrast to using EC probe and APC plasma flow. Arguments have been raised that compared to Nd:YAG laser, tissue effect of EC and APC is too superficial. Nd:YAG laser causes enormous heat sink effect, as photons of 1,064 nm deeply scatter in tissue for obtaining in depth necrosis. Electrons disperse, i.e., divergent flux, beneath the tissue layer leading to superficial crust of necrosis. End-stage lung cancer patients in the palliative setting have failed previous treatments, e.g., surgical resection and chemoradiotherapy. The central airway's anatomy is often changed, and together with the proximity of the major vessels, vigilance and expertise are required to avoid disaster. Tissue coagulation layer per layer, depending on assessment of tumor thickness, might well be more appropriate than instantly obtaining deep necrosis at once, e.g., using Nd:YAG laser. Slowly cooking can also be obtained using the blend mode of EC, i.e., applying the setting that uses alternating phases of high and lower voltages. With APC, one performs superficial welding of the target area layer per layer. The use of a monopolar probe allows palpation of the tracheobronchial wall giving important tactile feedback about target tissue and bronchial wall resistance in contrast to the noncontact firing of Nd:YAG laser.

APC can be used for burning superficial layer of early-stage mucosal cancer of several millimeter thickness. This is a comparable strategy to using CO_2 laser or ultraviolet light excitation of Photofrin II®, to deliberately obtain superficial rather than obtaining too deep necrosis.

Cryotherapy (see separate chapter) has the advantage of preserving bronchial cartilage with less scar tissue formation, which may be important in dealing with segmental and subsegmental location of tumors. However, results are not immediate, and tissue depth effect is difficult to predict while repeated cooling and thawing takes more time. The use of cryoablation has been recently reported in which larger surface area can be cryosprayed much faster.

Brachytherapy (see separate chapter) is a much more complex and expensive facility; special logistics and good collaboration with the radiation oncologist are essential. Even high-dose rate brachytherapy cannot provide immediate solace for emergencies, as several treatment fractions are needed. This is in stark contrast to heat tissue applications such as EC, APC, and lasers which can be obtained in a single treatment session. Therefore, tissue-heating methods, i.e., lasers, EC, or APC, are the only techniques that can provide immediate benefit for rapid recanalization of airway blockage.

Clinical Background

Unfortunately, interventional pulmonologists mostly deal with advanced-stage lung cancer with local tumor growth causing imminent suffocation and respiratory failure. Obstruction may be caused by intraluminal tumor growth as well as extraluminal airway compression by mediastinally located tumor and enlarged lymph node masses adjacent to the tracheobronchial tree, and bronchoscopic debulking or combined with stenting is the only treatment choice.

The majority of patients are usually presented with end-stage cancer and comorbidities; hence, their often poor condition and the negative selection of patients are such that morbidity or mortality of bronchoscopic intervention can be quite significant.

With such a clinical presentation, the easy logistics of EC and APC and familiarity of many with electrical appliances make their use for the clinical and outpatient setting more readily accepted.

Palliation and Treatment with Curative Intent

The effectiveness of interventional bronchoscopic treatment for immediate palliation of central airway obstruction has been established, often being the only treatment alternative left. Conceptually, the use of EC and APC is no different than applying Nd:YAG laser as described earlier. Easy logistics allow practical management in the daily practice of a bronchoscopy unit (2–4). As extensive investigations, e.g., CT scan, lung function measurements, and blood gas analysis, prior to intervention in patients with imminent respiratory failures are unfeasible, clinical findings of stridor and severe dyspnea justify immediate action. EC and APC can then be applied more easily for tumor coagulation prior to mechanical debulking and stenting.

EC and APC can better safeguard unexpected bleeding after taking biopsy as increasing number of patients at risk have cardiovascular comorbidities and are routinely taking aspirin and clopidogrel. Many educational workshops are now dealing with competency skill training that better prepare operator and team members to act properly and decisively in case of adverse events during bronchoscopy.

By either using the rigid scope or working through the endotracheal (ET) tube, the interventional pulmonologist can perform tissue coagulation with EC or APC probe and recanalize the central airways more effectively. The rigid scope with its larger working channel obviously better provides access for safer manipulation and primarily in safeguarding ventilation. Despite the wider acceptance of using only devices that suite the flexible bronchoscope, the blocking effect of the flexible bronchoscope can jeopardize safety. The proper execution of any interventional technique depends on the readiness and expertise of the team that is familiar with various procedures, including proficiency in using the rigid instruments. Therefore, one should always realize that technique per se is not the only factor that determines success regardless of the use of intraluminal tumor debulking that is easier to be applied.

Treatment for Intraluminal Non-lung Cancer Lesions

Interventional pulmonologists can also provide alternative treatment strategies after diligent consultation within the thoracic multidisciplinary team, for other intraluminally located tissue abnormalities.

Apart from lung cancer, involvement of central airways by tumor metastasis, benign lesions, and slow-growing lesions such as typical carcinoid, even malignant fibrosarcoma, does warrant a proactive role for the interventional pulmonologists to be involved in the care of these patients. The argument that a potential delay in surgery will jeopardize patients' outcome has not been proven in our longitudinal study with regard to bronchoscopic treatment of bronchial carcinoid. Given current knowledge on neuroendocrine tumors, this is in retrospect not surprising. Even after years of postponement, surgical resection would not have been different regarding extent of resection or outcome in the several cases that there was residual tumor or local recurrence in the bronchial wall. The various bronchoscopic techniques for benign processes must be seen in the same conceptual line as foreign body removal, in which surgical resection should remain the last resort. Any minimally invasive technique that can be first commenced in trying to solve the problem before performing major surgery is preferable rather than an immediate and hasty surgical approach.

Indeed, disease management has become a concerted effort between various disciplines by fully exploiting the different input from expert team members, including interventional pulmonologists. Increasing understanding about tumor behavior and clonal cell growth and behavior in current era of molecular biology and also in dealing with early-stage non-small-cell lung cancer is of paramount importance. The involvement of interventional pulmonologists in pulmonary medicine and medical oncology can be very supportive regarding early detection, staging, and treatment strategies, both for central airway and lung parenchymal abnormalities.

Future Strategies

Current interest in stage shift as the primary goal in a lung cancer screening setting poses a great challenge for its clinical management. As earliest stage cancer, i.e., carcinoma in situ and alveolar adenomatous hyperplasia, involves subcentimeter lesions, relying only to the gold standard of histology classification and surgical resection is currently inappropriate.

One may still argue that nonsurgical approaches are still not acceptable until data from phase III prospective trials have shown similar efficacy. However, the potential values of alternative techniques such as interventional bronchoscopy and radiation therapy for clinically unfit patients have been established.

While attention has been put on screening the population at risk for relatively healthy individuals, we must not forget that the clinical reality of increasing number of ageing patients with comorbidities remains the bulk of our care. This is a great challenge to further explore the many potentials of non- and minimally invasive techniques in better preserving quality of life and in improving the cost efficiency of our medical care system rather than relying on accepted standard diagnostic and therapeutic avenues including major surgical approach.

For relatively healthy individuals with early cancer that can tolerate surgical resection, lead time in carcinogenesis increases the potential long-term effect of overdiagnosis, if

combined only with aggressive management that has been implemented at the cost of quality of life.

The low positive predictive value of current diagnostic algorithms such as sputum cytology and low-dose spiral CT despite still requires much improvement. Although CT screening data show that more early-stage cancers are being detected and curatively treated, controversies about overdiagnosis are still heavily debated, and downstream morbidities and mortalities related to early detection programs may become a significant issue. Alternative approaches may significantly reduce downstream morbidities, mortalities, and costs not only in a screening program but also in our daily care of the patients by virtue of advancements of non- and minimally invasive technologies in terms of early detection, accurate minimally invasive staging, and local treatment that is potentially curative, as tumor stage is the most important determinant for cure.

Summary

Minimally invasive techniques in the field of interventional pulmonology have led to a better understanding of thoracic disease processes. Combined with current advances in non-invasive imaging, pathology, molecular biology, medical oncology, and radiation oncology, technical development allows us now to combine all expertise for optimally choosing a tailored and personalized strategy for each patient.

Proper consultations within members of the thoracic oncology and respiratory teams can better suit diagnostic, staging, and treatment incentives with optimal preservation of quality of life of the at-risk individuals involved. Increasingly in the ageing population, many individuals suffer from comorbidities, and a more coherent approach toward disease management is warranted.

Treatment use of electrocautery and argon plasma coagulation is just part of the armamentarium for optimizing our care in the daily routine of a bronchoscopy unit.

The encompassing issues of early detection, staging, tumor biological behavior, and treatment, however, are the important determining factors to be taken into account before making a proper decision about disease management that is aimed for a tailored strategy in each patient.

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Cryotherapy and Cryodebridement

33

Ramez Sunna

Introduction

Cryotherapy is the controlled application of extreme cold energy to diseased tissue, in which cells are destroyed by the formation of intracellular ice crystals. As a treatment modality, cold temperature energy has been in use as early as 2500 B.C., when the Egyptians used cold for its analgesic and anti-inflammatory properties.

James Arnott, an English physician, is accredited as the first clinician to use cold for palliation of tumors in the nineteenth century. He found that applying a mixture of salt and crushed ice locally reduced pain and hemorrhage, in addition to causing shrinkage of tumors. He used these solutions to treat breast, cervical, and skin cancers.

In 1877, liquefaction of gas under high pressure was made possible, paving the way for Campbell White from New York to use liquid air for treatment of epitheliomas and multiple skin conditions.

This modality was further improved by Dr. William Puse in Chicago with the introduction of solidified carbon dioxide (−78.5°C). Following World War II, liquid nitrogen (−196°C) was introduced and became the mainstay of treatment for many skin conditions.

The first reported use of endobronchial cryotherapy was in 1968 via a specially designed cryoprobe. This device was used through a rigid bronchoscope to relieve endobronchial obstruction by a tumor causing a postobstructive pneumonia.

In 1975, Sanderson et al. reported a case series using cryodebridement of endobronchial non-small-cell lung carcinoma, with 50% of patients having improved symptoms and a decrease in tumor size.

Due to the need of general anesthesia and rigid bronchoscopy as well as emergence of other endoscopic modalities such as neodymium-doped yttrium aluminum garnet (Nd:YAG) laser for the treatment of endobronchial obstruction, there was a relatively low interest among pulmonologist in cryodebridement until the introduction of a flexible cryoprobe (ERBE Inc., Marietta, GA) in 1994.

In current practice, airway cryotherapy is used primarily as one of several techniques and modalities to treat central airway obstruction. Alternatives include laser treatment, photodynamic therapy, brachytherapy, argon plasma coagulation, and electrocautery.

In many instances, the choice of modality depends on the availability of treatment options and on the clinical expertise of the physicians involved.

In this chapter, we will discuss the scientific principles of cryotherapy, indications for its use, the effectiveness of this modality, as well as provide a description of procedural techniques.

Scientific Basis

At the cellular level, applying extreme cold energy causes a cascade of destructive events (Table 33.1). Extreme cold leads to the formation of extracellular ice crystals. This causes an efflux of intracellular fluid which results in cellular dehydration and increased toxicity.

Rapid freezing also causes the formation of intracellular ice crystals that damage intracellular organelles such as the mitochondria and endoplasmic reticulum. This affects the acidity of intracellular fluid leading to further protein and enzyme damage.

Cryotherapy has a significant effect on microcirculation. Cold induces vasoconstriction, endothelial injury, and platelet plug formation leading to microthrombi with subsequent cellular death. This ischemic effect goes beyond the area of direct probe contact to affect the surrounding tissue. It is through this mechanism that malignant tissue, usually hypervascular, is rendered even more sensitive to cryotherapy.

Certain studies suggest that an immune-mediated tumoricidal mechanism through increased activated peripheral

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lymphocytes even affecting metastatic tumors exists; however, this mechanism is not well elucidated.

The effect of cryotherapy varies, depending on the sensitivity of the treated tissue. This is important when evaluating treatment potential as well as possible complications.

Mazur found the following tissues to be cryoresistant in vitro: fat, cartilage, nerve sheath, connective tissue, and fibrosis. Whereas, tumor, granulation tissue, skin, mucous membranes, nerves, and endothelium are cryosensitive. The inherent sensitivity of the targeted tissue mainly depends on the water content of the tissue. The more water content, the greater the sensitivity. Furthermore, multiple technical aspects influence the outcomes of cryotherapy:

Table 33.1 Cryotherapy: mechanisms of cellular damage

Temperature	Cellular effect
−5°C to −15°C	Formation of extracellular crystals causing compression and cell deformity
<−15°C slow cool	Efflux of intracellular fluid which results in cellular dehydration and toxic increase in intracellular electrolyte concentration
<−15°C rapid cool	Formation of intracellular crystals causing lysis of intracellular organelles, denaturation of proteins, and cell death
−50 to −80°C	Complete crystallization
Slow thawing	Migratory recrystallization: grinding action of ice movement through the cell

- Temperature for tissue destruction. Core tissue temperature must reach between −20°C and −40°C, as rapid freezing of tumors to −40°C or below is associated with 90% cell death.
- Rates of freezing and thawing. A process of rapid freezing and slow thawing is the ideal cycle.
- Number of freeze-thaw cycles.
- The mass of the tissue that is frozen.
- The contact area between tissue and cryoprobe.

The effects of cryotherapy on tracheal and bronchial mucosa have been studied in dogs. A return to normal macroscopic mucosa was seen after approximately 2 weeks. Microscopic epithelial and cartilaginous changes took closer to 6 weeks to resolve. The cellular damage and tissue destruction induced by cryotherapy continue over time. It takes hours to days for cellular necrosis to ensue. Necrotic tissue sloughs off within the airways and is often expectorated. Repeated bronchoscopic procedures for removal of debris are generally performed within 5–10 days.

Equipment Used in Endobronchial Cryotherapy

Endobronchial cryotherapy can be performed using a rigid, semirigid, or a flexible cryoprobe. The rigid and semirigid probes can only be used via a rigid bronchoscope, while the flexible probe can be used either through the rigid or flexible bronchoscope (Figs. 33.1 and 33.2).

Fig. 33.1 Rigid cryoprobe: Diameter 3 mm and length 530 mm (Source: From erbe-med.com http://www.erbe-med.com/de/medical-technology/public/Products/Cryosurgery/Cryo-Instruments/Probes-and-applicators/Cryoprobes-for-ERBOKRYO-CA/Bronchoscopy-cryoprobe.2448)

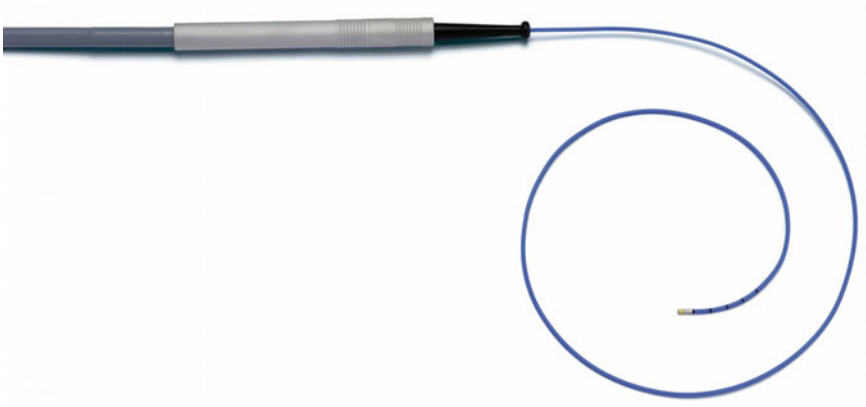

Fig. 33.2 Flexible cryoprobe: Diameter 2.4 mm and length 900 mm (http://www.erbe-med.com/de/medical-technology/public/Applications/Pneumology/Tracheabronchial-biopsy-with-flexible-cryo-probe.993)

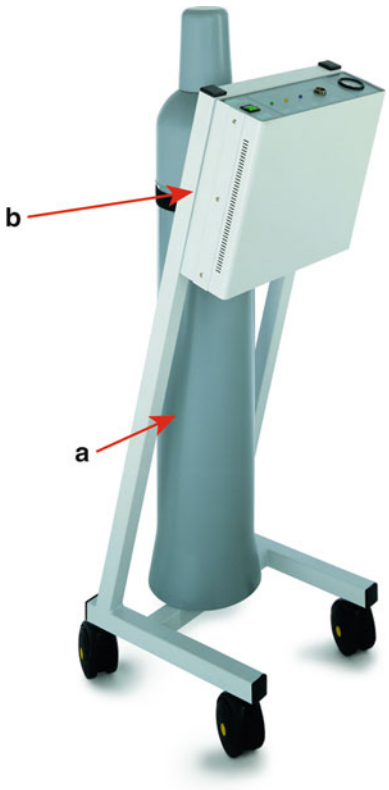

Fig. 33.3 Console and gas cylinder: (**a**) N_2O gas cylinder; (**b**) cryo-console (http://www.erbe-med.com/de/medical-technology/public/Products/Cryosurgery/Cryosurgery-Units/ERBOKRYO/ERBOKRYO---CA.1154)

Cryotherapy units contain a console that regulates the flow of cryogen (Fig. 33.3). This console is typically controlled via foot pedal. Cryoprobes are designed to deliver the highly pressurized liquid cryogen to the tumor. Rigid probes are larger and may contain a reheating system which, in addition to freezing, allows for rapid reheating. This results in a more rapid thawing phase, as compared to that of the flexible probe, where spontaneous thawing must occur, resulting in a longer procedure time.

Several cooling agents are in use in general cryotherapy. For endobronchial lesions, nitrous oxide (N_2O) is the most widely used. Coolants are stored at room temperature under high pressure in liquid phase. The passage of the liquid through the probe from high pressures to atmospheric pressure causes it to expand, resulting in a temperature of −89°C at the tip of the probe.

Indications for Endobronchial Cryotherapy

Cryotherapy is one of multiple methods available to the bronchoscopist. Traditionally, it has been used as a therapeutic tool for the treatment of patients with central airway obstruction. Recently, there is a growing interest in its diagnostic potential, and it is also being used to obtain endobronchial and transbronchial biopsies. When used in the treatment of benign and malignant central airway obstruction, it can be used in lieu of or in conjunction with other modalities of endobronchial treatment, such as mechanical debridement, laser therapy, electrocautery, argon plasma coagulation, brachytherapy, or photodynamic therapy.

Benign Airway Obstruction

Using the cryoprobe for foreign body removal is especially effective when the object has high water content. Mucus plugs, blood clots, aspirated food matter, or pills freeze and adhere well to the cryoprobe, allowing for their extraction frozen to the cryoprobe while the gas is still activated. Objects with a more solid consistency, such as teeth or metal parts, are less cryo-adherent, making removal using the cryoprobe less efficient.

Granulation tissue is highly cryosensitive. Cryotherapy is used especially in the treatment of posttransplantation-, tracheostomy-, or stent-induced granulation tissue formation. It is particularly useful when treating granulation tissue formation in covered metallic stents where other modalities such as electrocautery, argon plasma coagulation, or Nd:YAG laser may be contraindicated.

Removal of benign airway tumors such as endobronchial lipomas and treatment of weblike stenoses has also been reported. However, benign strictures composed mainly of fibrous tissue are not amenable to cryotherapy.

Malignant Endobronchial Disease

Approximately one third of lung cancer patients have central airway disease on presentation (Fig. 33.4). Their symptoms usually include cough, hemoptysis, dyspnea, and recurrent postobstructive pneumonias.

Unfortunately, most patients at this stage are inoperable. Systemic chemotherapy is usually ineffective for obstructive disease, particularly in non-small-cell lung cancer. Radiation therapy is slow and is limited by the total dose that can be delivered. It is under these circumstances when endobronchial debridement takes on a major role.

It is important to define the precise role of cryodebridement in lung cancer in order to be able to select the appropriate candidate for cryotherapy. First, a histological diagnosis must be obtained. Surgery with curative intent should be the initial choice. It is only when this goal is not achievable or when palliation is the objective that cryotherapy becomes a viable option.

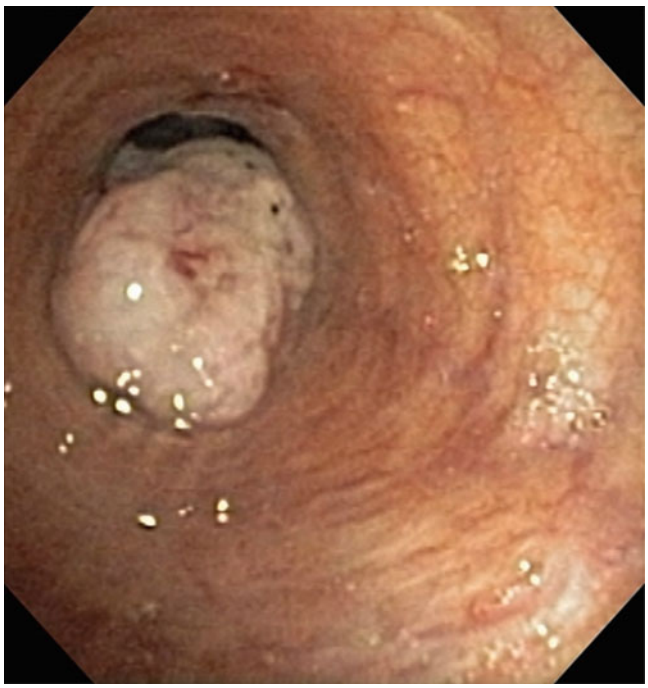

Fig. 33.4 Endobronchial tumor. A 64-year old man with squamous cell carcinoma involving the left mainstem bronchus

The patient's symptoms should be attributable, at least in part, to an endobronchial lesion. The lesion must be accessible to the cryoprobe through the bronchoscope, and the patient should be willing and able to undergo the procedure. Patients with short polypoid lesions with patent distal airways are the ideal candidates for endoscopic intervention.

In patients in respiratory distress, with acute airway emergencies, where immediate recanalization is the main objective, other modalities, such as mechanical debridement, laser therapy, electrocautery, or argon plasma coagulation, are generally preferable, for their immediate effect over cryodebridement, despite recent reports of rapid cryodebridement techniques.

The effectiveness of cryodebridement is limited in long-segment, submucosal, and extrinsic tumors. For mixed tumors, and especially those causing extrinsic compression, treatment with airway dilatation followed by placement of an airway stent is usually warranted. However, cryotherapy is used effectively for the treatment of tumor ingrowth or granulation tissue complicating stent placement.

Cryotherapy Technique

Standard pre-procedure evaluation and preparation are undertaken. A thorough symptom evaluation, assessment of performance status, pulmonary function test, and thoracic computed tomography are usually performed.

Whenever there is a clinical suspicion of increased bleeding tendency, the patient's coagulation profile and platelet count are checked. Full anticoagulation therapy with heparin, low-molecular-weight heparin, or warfarin is temporarily held prior to procedure. Clopidogrel therapy is also held for 5–7 days prior to procedure. Aspirin treatment is generally continued.

Prophylactic antibiotics are administered in cases where there is a high risk of infective endocarditis.

Tumor Cryodebridement

Cryotherapy can be delivered via rigid or flexible bronchoscopy. Standard anesthesia for either of the respective bronchoscopy procedures selected above is administered, and regular monitoring is conducted. Although some experts report performing this procedure under moderate sedation using a flexible bronchoscope, our practice is to perform it in the operating room under total intravenous anesthesia via a rigid bronchoscope using a rigid barrel as a conduit for the flexible bronchoscope. This will allow us to have a secure airway and, at the same time, reach the segmental and subsegmental levels if clinically necessary.

The procedure starts with a full inspection of bronchial segments. After the endobronchial lesion has been identified, the tip of the bronchoscope is positioned around 0.5–1.0 cm proximal to the lesion.

The cryoprobe is then inserted through the working channel of the bronchoscope. When using a flexible scope, it is kept approximately 4 mm away from the tip of the scope. Under direct visualization, the cryoprobe is placed in direct contact with the tumor, either perpendicularly or tangentially. The cryoprobe may also be pushed into the tumor, producing circumferential freezing of maximal volume.

Using the foot pedal, the bronchoscopist activates the cryoprobe. Gas will cool the probe tip to ~−89°C. Freezing is continued for 30 s, after which the foot pedal is released, and passive thawing is allowed.

This freeze-thaw cycle is repeated an average of three cycles at each site, sometimes varying according to the size and depth of the lesion. The tip of the cryoprobe is moved to an adjacent area, and the above actions are repeated until the entire lesion is completely frozen (Fig. 33.5 a, b). Suctioning of blood or secretions between applications of the cryoprobe is sometimes necessary.

Any resultant necrotic tissue can be removed by suctioning, by using biopsy forceps, or by freezing the tissue to the cryoprobe and retracting the cryoprobe prior to thawing, but while maintaining probe material adherence.

Due to delayed sloughing of treated tissue, a repeat bronchoscopy is performed in 5–10 days. This is done to remove necrotic tissue and clear any secretions that would otherwise lead to symptoms of cough and dyspnea, in addition to distal airway obstruction and atelectasis.

A newer technique of cryodebridement is increasingly being used. This technique has the potential advantage to

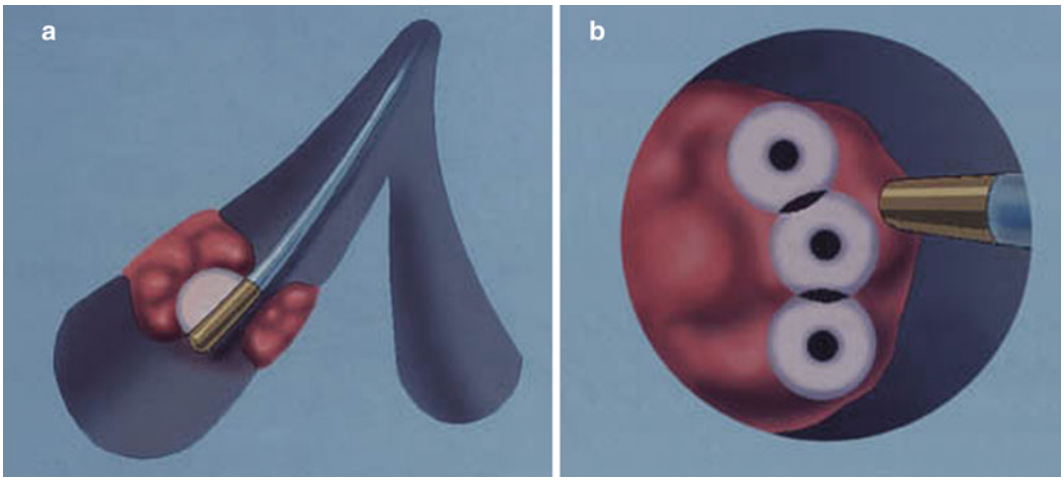

Fig. 33.5 Cryotherapy technique: (**a**) cryotherapy applied to the tissue using the probe side; (**b**) cryotherapy applied to the tissue using the tip of the probe. Reapplication to the same area after thawing allows for a deeper freeze and tissue destruction (Sheski FD, Mathur PN. Cryotherapy, electrocautery, and brachytherapy. Clin Chest Med. 1999;20:123–38. Reprinted with permission)

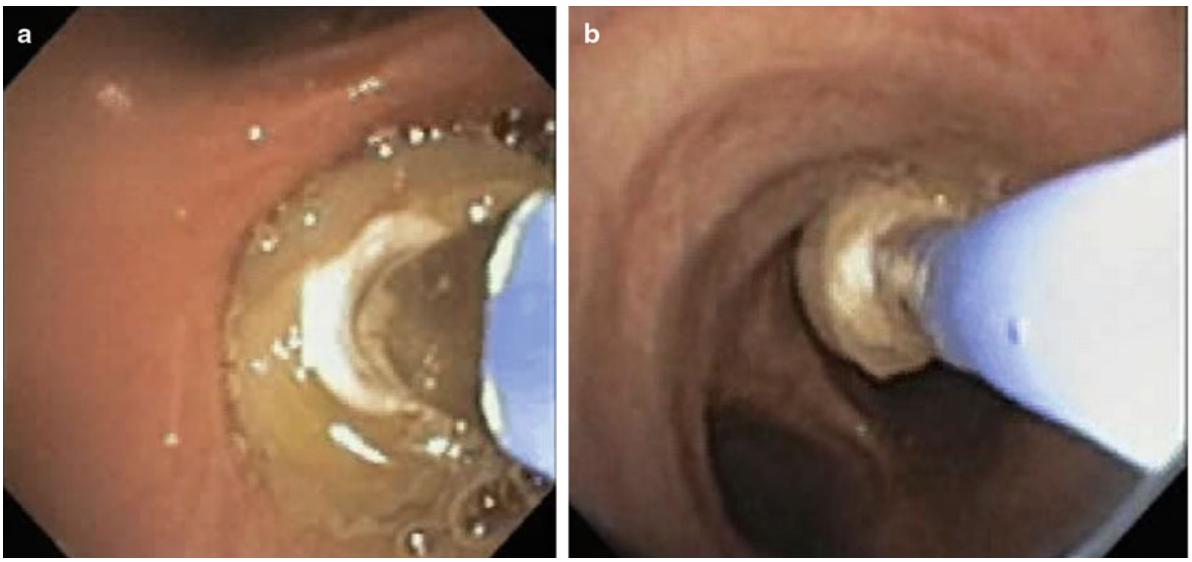

Fig. 33.6 Endobronchial cryodebridement. A 75-year old man with metastatic renal cell carcinoma to the *right lower* lobe: (**a**) tip of the cryoprobe frozen to the tumor; (**b**) tumor being pulled *en bloc* attached to the cryoprobe along with the bronchoscope (Photographs courtesy of Dr. Martin Mayse)

decrease procedural time and achieve faster results, with less need of repeated procedures.

The airway is initially secured via intubation using an endotracheal tube or with a rigid bronchoscope. As in the traditional technique, a flexible bronchoscope is inserted and directed toward the tumor. Next, a flexible cryoprobe is passed through the working channel of the flexible bronchoscope, under direct visualization, into the tumor.

Noting freezing of tumor tissue, the tip of the cryoprobe is cooled for 5–20 s. At this time, the probe is pulled strongly, and the cryoprobe with frozen tissue attached to its tip is withdrawn, along with the bronchoscope (Fig. 33.6).

The frozen tumor tissue is thawed off the probe in a water basin. This process is repeated until adequate debridement and canalization of the airway have been achieved.

Endobronchial and Transbronchial Biopsy Techniques

Using the cryoprobe to biopsy endobronchial lesions has the advantage of providing hemostasis while preserving the architectural integrity of tissue specimens (Fig. 33.7).

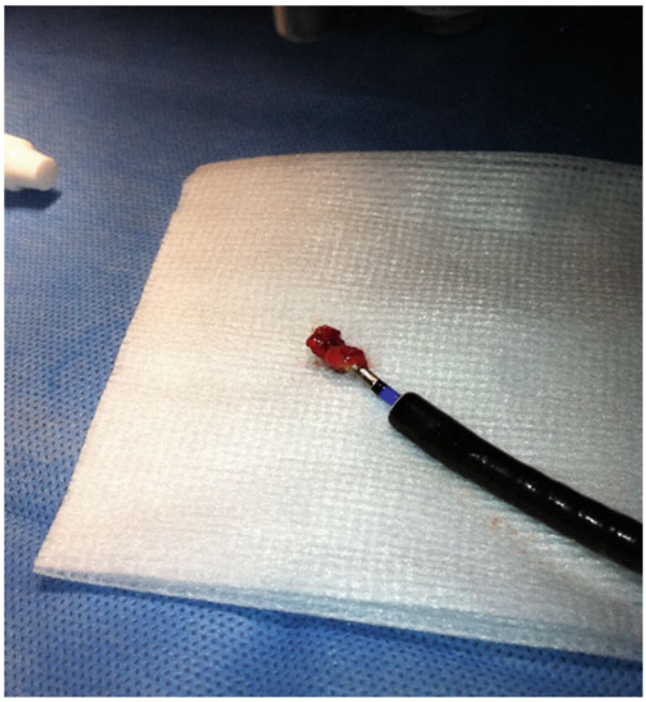

Fig. 33.7 Extracted tumor tissue. This shows the extracted tumor tissue that is attached to the cryoprobe (Photograph courtesy of Dr. Adnan Majid, BIDMC, Boston, MA)

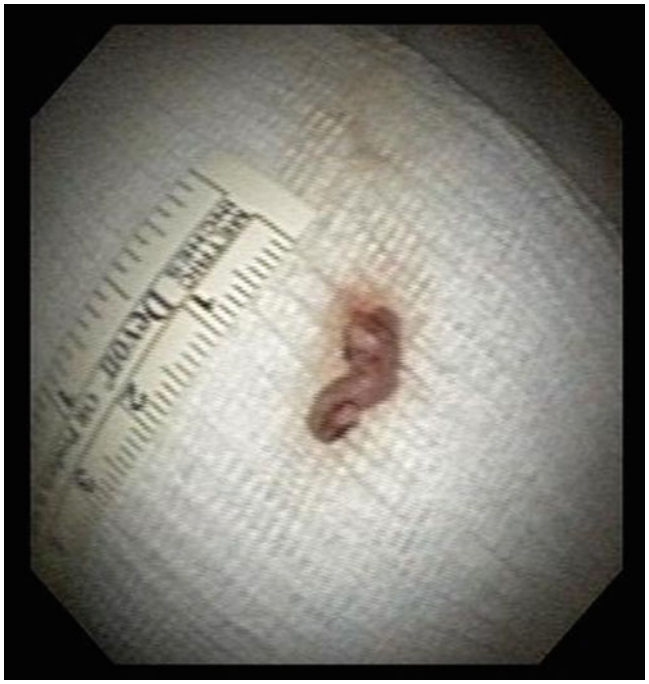

Fig. 33.8 Transbronchial cryoprobe lung biopsy. Single irregular tan-pink soft tissue fragment measuring 1.4×0.5×0.4 cm in a patient with diffuse lung disease that was obtained using the transbronchial cryobiopsy technique (Photograph courtesy of Dr. Adnan Majid, BIDMC, Boston, MA)

When performing an endobronchial biopsy, the cryoprobe is passed through the working channel of the bronchoscope and advanced 4 mm beyond the tip of the bronchoscope. Direct contact between the probe and the lesion is achieved. Tissue is frozen to the cryoprobe tip by activating the probe for approximately 5 s. While maintaining probe activation, the cryoprobe, with the frozen sample attached to it, is retracted back through the working channel of the bronchoscope. Alternatively, the cryoprobe with the frozen tissue attached to it can also be removed along with the flexible bronchoscope. When using this latter technique, patients are preferably intubated to allow multiple biopsies, as well as to avoid repeated bronchoscopic intubations.

Schumann et al. prospectively evaluated and compared the diagnostic yield and safety of cryobiopsy and forceps biopsy in 55 consecutive patients. The diagnostic yield for cryobiopsy compared with forceps biopsy was higher (89% vs. 69%, $P<0.05$). Additionally, quantitative image analysis showed significantly larger biopsies and artifact-free tissue sections for cryobiopsy specimens ($P<0.0001$). Reported complications include mild bleeding in 3.7%, moderate bleeding in 1.0%, and severe bleeding in 0.3%, which were similar to those seen with endobronchial forceps biopsy.

Transbronchial lung biopsy is the method of choice for obtaining parenchymal tissue specimens. However, a definitive diagnosis based on histological analysis of these specimens is often not possible primarily due to the small size of the biopsies, as well as alterations caused by the pressure of the forceps on the tissue. Transbronchial biopsies using the cryoprobe are believed to increase diagnostic yield by obtaining larger and better-preserved specimens (Fig. 33.8).

With the patient intubated and after endoscopic evaluation of the bronchial tree, the bronchoscope is wedged in the selected segment based on prior imagery. The cryoprobe is introduced through the working channel of the bronchoscope and directed to the previously targeted area, preferably under fluoroscopic guidance (Fig. 33.9). Once in position, the probe is cooled for 4 s by activating the cryoprobe using the foot pedal, and the tissue is frozen to the tip of the probe.

The cryoprobe, with the tissue sample still attached to it, is then removed, along with the bronchoscope. The tissue sample is subsequently allowed to thaw off the cryoprobe and is placed in formaldehyde solution.

Babiak et al. conducted a prospective study on 41 patients with diffuse lung disease. Specimens obtained with a biopsy forceps were compared with those from a cryoprobe. The mean specimen area was 5.8 mm^2 for samples taken by forceps compared to 15.11 mm^2 obtained using the cryoprobe ($p<0.01$). Two patients had a pneumothorax which resolved by tube thoracostomy. Biopsy-associated bleeding was

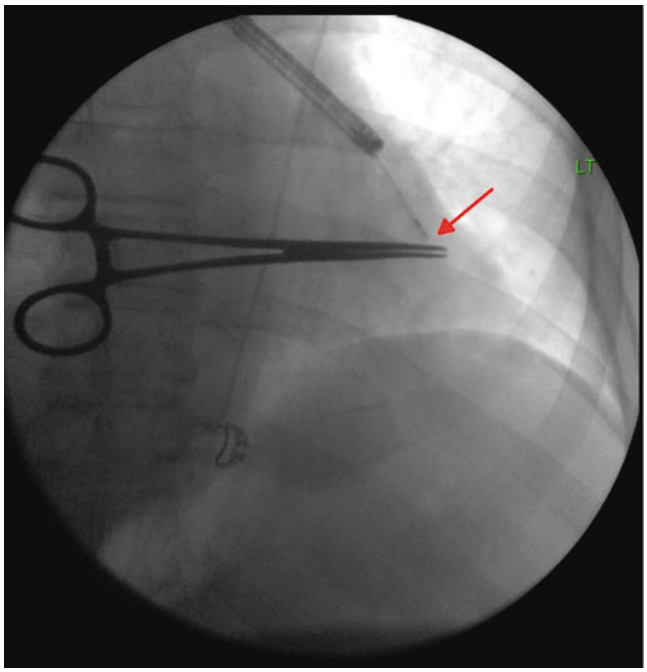

Fig. 33.9 Fluoroscopy-guided transbronchial cryoprobe biopsy: Cryoprobe (see *red arrow*) is directed to the *left lower* lobe for a transbronchial biopsy. The lesion had been previously localized using a radial endobronchial ultrasound. The tip of the Kelly clamp was used to mark the site in a patient with 1.3-cm LLL nodule (Photograph courtesy of Dr. Adnan Majid, BIDMC, Boston, MA)

self-limited. Authors concluded that transbronchial cryobiopsy allows obtaining large samples of lung parenchyma safely and in a substantial number of cases, this technique contributed to a definitive diagnosis.

Although the optimal number of biopsies to be performed has yet to be determined, successful specimen collection is based on the size of the specimens obtained and the patient's tolerance of the procedure, with two specimens removed being the typical minimum number required for further testing.

Clinical Outcomes of Cryodebridement

The outcome of cryotherapy is assessed based on subjective symptomatic improvement, physiologic changes on pulmonary function testing, as well as radiologic and endoscopic appearance.

Clinical outcomes have been reported using both rigid and flexible cryoprobes, with most initial data being based on the use of rigid probes and more recent experience using flexible probes. Outcomes did not differ significantly based on the type of probe used, but rather on the location and nature of the lesion, as well as the number of cryodebridements performed.

Experience with cryotherapy continues to grow and improve. Cumulative data from published studies indicates that subjective improvement in dyspnea is expected in 70–86% of patients, resolution of hemoptysis in 62–100% of patients, and improvement in Karnofsky performance scale in 63% of patients.

Improvement in oxygenation is noted in more than 66% of patients. In a study of 521 patients, FEV1 and FVC measurements improved by a mean of 0.12 and 0.2 L, respectively.

In all reviewed reported cases of benign lesions that were treated with cryotherapy, restoration of airway patency was almost universal. Based on the technique used and the number of treatments conducted, airway patency was restored in 22–83% of malignant lesions treated with cryotherapy. Higher rates were reported with the newer immediate cryocanalization technique or with repeated treatments.

Safety Profile

Cryotherapy is considered a safe diagnostic (endobronchial and transbronchial biopsy) and therapeutic (endobronchial debridement) bronchoscopic tool. Occasionally, it is performed in high-risk patients having significant underlying cardiopulmonary disease.

Respiratory failure is the most common cause of mortality associated with cryodebridement. In Maiwand's case series of 521 patients, 3% of patients developed respiratory distress postoperatively which eventually resolved. In-hospital mortality rate was 1%, all secondary to respiratory failure; 2% developed arrhythmias. Bleeding is usually mild and generally easily controlled by suction, cryoapplication, iced saline, or topical epinephrine. Airway edema and bronchospasm may occur, and some experts give corticosteroids for 24-h post-procedure, although the benefit is not proven. Precaution to prevent spillage of purulent secretions from a postobstructive pneumonia should be taken by placing the patient in the lateral decubitus position with the affected lung down and applying adequate suction during the procedure. Fever has been reported as a minor complication and can be prevented by the administration of prophylactic corticosteroids or treated with antipyretic agents.

Risk of airway perforation is lower than with other modalities, such as laser debridement or electrocautery, due to the relative cryoresistance of cartilage and fibrous tissue. Delayed sloughing can lead to worsening symptoms, atelectasis, and postobstructive pneumonia; however, this is generally avoidable by performing a repeat bronchoscopy within 5–10 days after the cryotherapy.

Training Requirements

Dedicated operators performing cryotherapy should have extensive experience in flexible bronchoscopy and management of central airway lesions. The American College of Chest Physicians and the European Respiratory Society guidelines for interventional procedures state that trainees should perform at least ten procedures in a supervised setting to establish competency. To maintain competency, dedicated operators should perform at least five procedures per year.

Conclusion

Endobronchial cryotherapy is a safe, relatively inexpensive technique that has multiple uses, from improving diagnostic yield and safety in endobronchial and transbronchial biopsies to debridement of malignant and benign airway tumors.

The procedure can be performed via rigid or flexible bronchoscopy which further allows for expanded clinical considerations.

Compared to thermic tumor debridement techniques, cryotherapy has the advantage of a more favorable safety profile, with less risk of airway perforation, air embolism, or endobronchial fires. In addition, cryotherapy provides easier setup and procedural technique.

Disadvantages are the potential need for repeated procedures, some delayed effects of treatment, and the relative resistance of certain benign tumors to cryotherapy, in comparison to thermal techniques.

Cryotherapy remains an underutilized treatment method that can be an integral component in the multimodality approach to the optimum effective management of tracheobronchial obstruction.

Acknowledgment I would like to gratefully acknowledge Dr. Adnan Majid for his helpful contributions and enormous support during the process of writing this manuscript.

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Microdement

34

William Lunn

Introduction

Earlier chapters in this text have reviewed the natural history and pathogenesis of central airway obstruction; that is not the objective here. The reader is reminded that although central airway obstruction commonly manifests as cough and dyspnea, high-grade obstruction of the trachea and main bronchi may cause severe dyspnea, postobstructive infection, and respiratory embarrassment. It is in this setting that an interventional pulmonologist, otolaryngologist, or thoracic surgeon is consulted to assist with the rapid reestablishment of a patent airway. Such patients may require supplemental oxygen, suffer from coexisting chronic lung disease, and may have other comorbidities that add risk to any planned intervention. While shorter procedure times are associated with fewer complications, traditional methods employing forceps dissection and thermal modalities with flexible or rigid techniques are often time consuming.

There is a need to safely remove obstructive tissue in an expeditious manner. Enter the microdebrider: a long hollow metal tube with a distal spinning blade coupled to suction. Microdebriders are employed under microscopic guidance with suspension laryngoscopy or under telescopic guidance with rigid bronchoscopy. During dissection, tissue is drawn up and into the blade so that the physician can avoid inadvertent damage to the normal airway wall. Debris, mucous, and blood are rapidly removed from the operative field, giving the physician an excellent view of the operative field as debridement is being carried out.

There are three central components to a microdebrider: a disposable blade, a handpiece, and a console. Microdebriders are now available from a variety of manufacturers. Airway blades (Fig. 34.1) come in a variety of lengths (8–45 cm), diameters (2.9–4 mm), shapes (straight vs. angled), and contours (smooth vs. serrated). The blades attach to a handpiece (Fig. 34.2) which drives the blade and couples suction to the system. The console (Fig. 34.3) controls the direction of rotation of the blade (forward, reverse, or oscillating) and the speed of rotation. Activation of the console is controlled via a foot pedal.

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History of the Microdebrider

Dr. Jack Urban is credited with the development of the first microdebrider. In the mid-1960s, Urban became interested in a better way to resect tissue in a small operative field and began work on a prototype of what he later called a "rotary vacuum dissector." After further development, Urban secured a patent for his device in 1969. Though initially met with limited enthusiasm, the rotary vacuum dissector eventually gained credibility with physicians. Dr. William House began using the device in the early 1970s to remove acoustic neuromas. By the early 1980s, orthopedic surgeons began to employ the device to carry out arthroscopic procedures. The 1990s witnessed an explosion in the use of microdebriders, in part because of improved technology in debriders, but also in operating telescopes and microscopes. Currently, microdebriders are routinely employed by surgeons in a variety of procedures including nasal/sinus surgery, pharyngeal surgery, laryngeal surgery, tonsillectomy/adenoidectomy, airway interventions, joint surgery, and liposuction.

Proper Operative Technique

Patients undergo general anesthesia since microdebriders must be used with either a rigid bronchoscope or suspension laryngoscopy. The anesthesiologist and surgeon should develop a plan preoperatively and work in concert during the case to assure the best results. Once the case is underway, a telescope or microscope is employed in tandem with the

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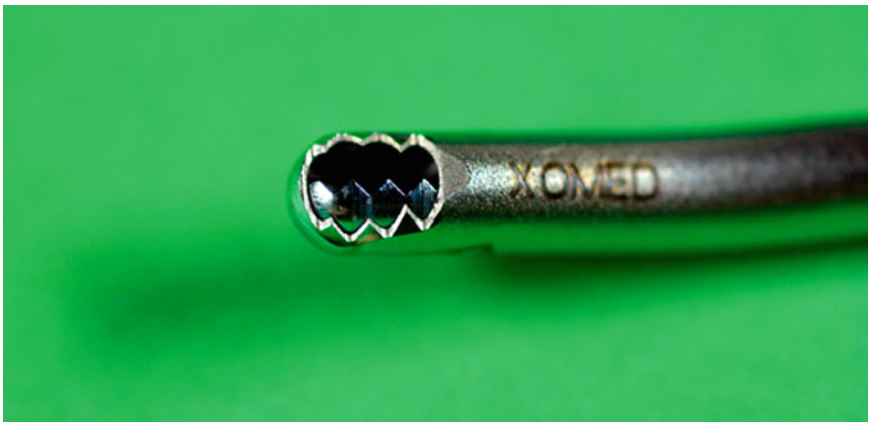

Fig. 34.1 Serrated microdebrider blade

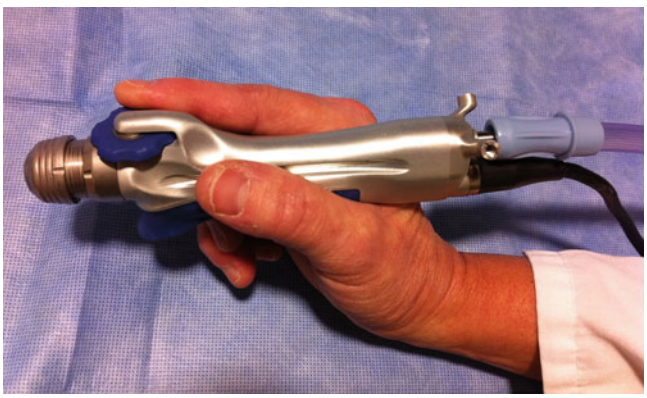

Fig. 34.2 Handpiece with suction tubing attached

microdebrider to give the surgeon proper visualization. This requires a bronchoscope, tracheoscope, or laryngoscope of sufficient diameter to accommodate the instruments. Commercially available airway blades range from 2.9 mm to 4 mm in diameter, while telescopes are typically 3 mm to 6 mm in diameter.

Scopes are selected based on the size of the patient and the anatomy of the lesion. For example, a mainstem bronchial lesion in an average-sized adult would be approached with a 12 mm diameter bronchoscope, whereas a proximal tracheal lesion might be approached with a 12 mm diameter tracheoscope. Lesions in the glottis or subglottis may be treated employing a Dedo laryngoscope.

Friable lesions are best resected with a serrated blade in an oscillating mode, while fibrous tissue is more amenable to a smooth blade with a unidirectional mode. Rotational speed controls the amount of tissue drawn into the blade aperture. Slow speeds (500–1,000 rpm) result in bigger tissue bites, while faster speeds (>1,000 rpm) result in smaller bites. Tissue is drawn into the blade aperture with suction; the operator can avoid inadvertent resection of normal airway tissue by employing this property to advantage. Newer microdebrider systems allow the surgeon to alter the direction of the tip of the blade by manipulating a dial on the handpiece, allowing even finer control of the blade aperture. Thermal modalities, such as argon plasma coagulation (APC), electrocautery (EC), or neodymium-doped yttrium aluminum garnet laser (Nd:YAG), must be available to deal with excessive bleeding should it occur. Employing rigid scopes wide enough to accommodate all the necessary instruments is paramount (Fig. 34.4).

As with any surgical tool, misuse of the microdebrider may result in complications. There are three simple principles of microdebrider use in the airway. First, the surgeon should never deploy the blade past their field of vision: one cannot control what one cannot see. Figure 34.5 demonstrates proper positioning of the blade relative the operator. Second, the surgeon should avoid putting pressure on the airway wall with the microdebrider as this may lead to normal tissue being drawn into the blade aperture. Third, one must deploy the blade parallel to the airway wall, never perpendicular, as this may result in airway perforation. Perhaps the most-reported complication of employing microdebriders in all applications is accidental resection of or damage to surrounding normal tissue. Complications can be easily avoided by adhering to the principles above.

Evolution of Use in the Airway

Since the microdebrider is a tool commonly employed by ENT surgeons in other applications, it should not be surprising that they found their way into the airway. In fact, surgeons had been using microdebriders for laryngeal problems and had even devised special “skimmer blades” for use on and around the vocal cords. Perhaps the best early demonstration of the utility of the tool in the airway was published by Simoni et al. in 2003. They described their experience using the microdebrider to rapidly establish a patent airway in 27 patients with advanced laryngotracheal carcinoma. All

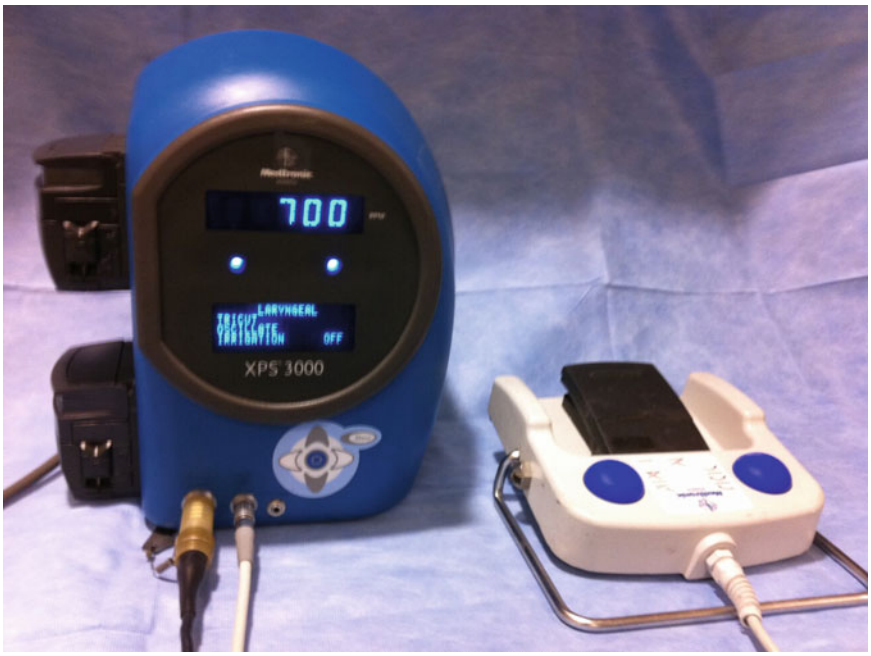

Fig. 34.3 Console and foot pedal

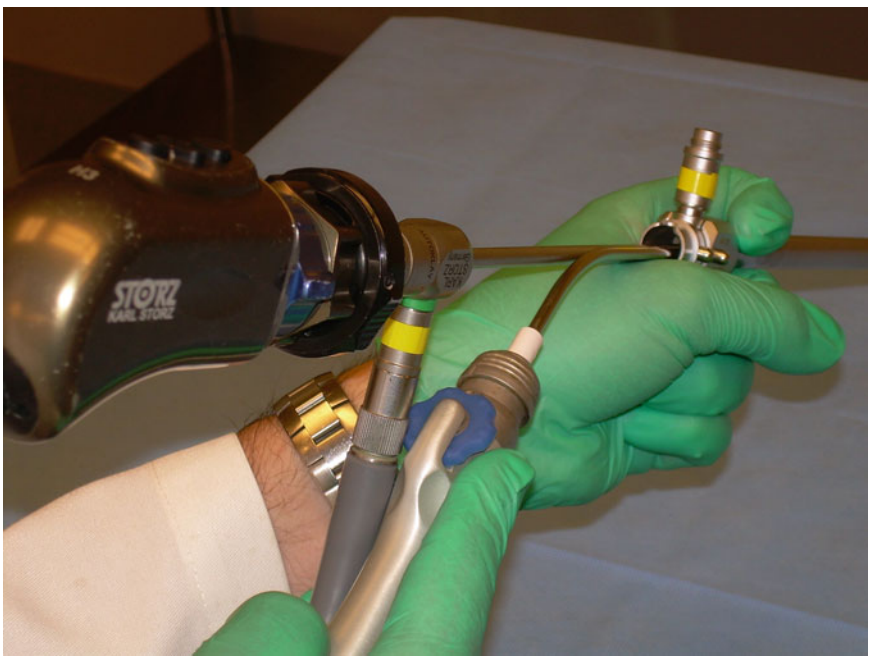

Fig. 34.4 Surgeon's view of bronchoscope, microdebrider, and telescope

their patients received postoperative radiation therapy, with 24 of 27 avoiding tracheotomy. These results were so impressive that other surgeons were inspired.

Soon after learning of Simoni's success, the Ernst Interventional Pulmonary group employed the technique to deal with obstructive suprastomal granulation tissue in patients with tracheotomies. Encouraged by their ability to rapidly remove obstructing tissue and restore phonation in their patients, they hypothesized that the technique could be employed in the distal trachea and lower airway to relieve obstruction due to a variety of pathologies.

Ernst, Lunn, and Morice piloted the tool extensively from 2003 to 2008, approaching a variety of benign and malignant lesions as their confidence and experience with microdebriders grew. Impressed by the control of tissue removal and the rapidity of dissection, investigators were soon tackling the

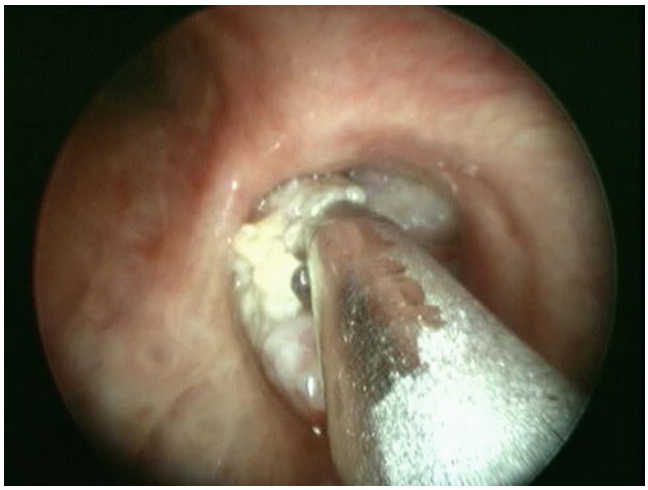

Fig. 34.5 Microdebrider resecting *right* mainstem bronchus tumor

most difficult and friable lesions with the technique. Pathologies ranging from subglottic granulation tissue to renal cell carcinoma were treated with success. During this "middle period" of airway microdebrider work, many lessons were learned by investigators. The operating techniques described above represent a distillation of the most valuable lessons learned.

Since 2008, numerous studies have appeared in the adult literature describing the use of microdebriders for assistance with removing foreign bodies, dealing with stent-related granulation tissue, debulking malignant airway tumors, and removing airway papillomas. Many physicians have described the use of thermal modalities in concert with the microdebrider, leading operators to ask if the next generation of microdebriders will incorporate electrocautery as a function, much like the suction Bovie.

Comparison to Traditional Techniques in the Respiratory Tract

The Campisi group reported in 2009 on their prospective study of the microdebrider vs. the CO_2 laser for removal of vocal papillomas. They studied 11 patients, performing postoperative perceptual and acoustic voice analysis following surgery. The 5 patients in the microdebrider group achieved superior postoperative voice outcomes compared to the 6 patients in the CO_2 laser group.

The microdebrider has been widely used for tonsillectomy with many studies done to compare more traditional techniques. In 2009, Wilson et al reported their experience with 156 patients undergoing tonsillectomy with either the microdebrider, Coblator, or Bovie. This prospective, randomized study was designed to compare the techniques by measuring intraoperative time, morbidity, complications, and cost. The Coblator and microdebrider were superior to Bovie in all areas, with the microdebrider demonstrating superiority to the Coblator only by lower cost. Gallagher et al., in January of 2010, reported their experience with complications after tonsillectomy in 4,776 patients employing the same three techniques: microdebrider, Coblator, or Bovie. The study was designed to compare the rates of major postoperative complications, bleeding, and dehydration. The complication rate for the microdebrider technique was significantly less than that of procedures done with the other two techniques. The results of the study influenced the authors to conclude that the microdebrider was the preferred instrument for tonsillectomy.

Investigators have also compared the microdebrider with laser and radiofrequency ablation (RFA) for performing turbinate reduction. Lee et al. performed a case control study on 37 patients undergoing turbinate reduction: 22 were done with a microdebrider and 15 were done with a laser. Patients were evaluated by endoscopic measurements before and after surgery. Patients in the microdebrider group achieved a superior result, which was especially evident if there was any bone hypertrophy in addition to nasal mucosal hypertrophy. Cigni et al. published a prospective study of 268 patients undergoing inferior turbinoplasty done either with a microdebrider or radiofrequency ablation (RFA). The 124 patients in the microdebrider group had superior patient satisfaction and rhinomanometric measurements as compared to the 144 patients in the RFA group. The differences between the groups were statistically significant. Based on their experience, the authors felt the microdebrider was superior to the RFA.

Conclusions

The microdebrider is a very useful tool for rapidly removing obstructive tissue from the airway. The ability to simultaneously remove blood and tissue debris gives the operator a greater degree of control of the operative field. In the upper respiratory tract, studies have proven it to be safe, cost effective, and precise. There are no comparative studies of the microdebrider to other modalities in the lower airway. The microdebrider has what many perceive to be one principle disadvantage, that of requiring rigid instrumentation and general anesthesia. Additionally, one must be aware that the microdebrider is so effective at removing tissue that it can remove normal tissue if mishandled. For the operator experienced with rigid techniques, it is a most satisfying modality.

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Use of Medical Lasers for Airway Disease

35

Jeffrey B. Hoag

Introduction

Since the original case reports in the mid-1970s, utilization of lasers for tracheal and central bronchi lesions has been the cornerstone for the airway interventionalist. The initial reports utilized CO_2 lasers that had been designed for non-airway applications; however, there now exist other laser platforms with more dynamic properties increasing the therapeutic arsenal. Several types of lasers have been used in the airway, of which, the neodymium-doped yttrium aluminum garnet (Nd:YAG) has risen as the major workhorse for airway intervention in interventional pulmonology. Over the last 30 years, our collective understanding of the indications for laser airway use, complications and safety concerns, and outcomes of patients receiving this therapeutic modality has advanced tremendously. Large cohort studies from several centers around the world have catalogued complication rates and outcomes, and our knowledge continues to grow. This chapter will provide an understanding of the physics of medical lasers, types of lasers commonly employed, descriptions of indications, contraindications, and complications of therapies. Moreover, this chapter will highlight some of the collective knowledge on outcomes of laser airway therapy as well as a brief discussion of essential training recommendations.

Laser bronchoscopy treatment of airway-obstructing lesions has been demonstrated to improve quality of life through improvement in respiratory symptoms and improve functional status and, in some studies, has been shown to lengthen life.

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Basics of Lasers

Laser, or light amplification by stimulated emission of radiation, produces high energy due to inherent properties. The cornerstones of laser properties are three distinct phenomena: coherence, collimation, and monochromaticity. These properties are characteristic to the medium used for lasing. First, coherence refers to the property of laser light travel in parallel phase in time and space. Next, collimation refers to the single directionality of laser light allowing for persistence of energy over much longer distances. Finally, monochromaticity refers to the fact that laser light has a single wavelength. In contrast to visible light, that is made up of multidirectional, broad spectral energy that is out of phase, lasers are ideal for controlled, aimed, and tuned applications that require high energy. The particular characteristics of lasers are determined by the medium that produces the laser light due to its physical properties as determined by the wavelength of light emitted (Table 35.1). Laser applications in medicine are subject to constraints of anatomy and physical properties of the tissue–laser interactions.

How Do Lasers Work?

For the emission of laser light, a stimulus is used to apply energy to the lasing medium. The stimulus that excites the medium can be another laser, a flash lamp, or an intense electrical current. Energy is transferred from the stimulus to the lasing medium leading to movement of electrons to a more unstable, excited state. With the drop in energy of the electron back to its original state, photons, or small light particles, are emitted with a frequency and wavelength that are characteristic to the lasing medium. This emission of photons is the laser light which is directional, in phase, and monochromatic. The lasing medium is placed into a cavity with mirrors at either end, one that is completely reflective and one that is partially reflective (Fig. 35.1). As the photons

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Table 35.1 Characteristics of medical lasers

Laser	Wavelength (nm)	Delivery device	Scope	Depth of penetration	Uses	
					Coagulation	Cutting
Nd:YAG	1,060	Quartz fiber	RB/FB	0.5–1.5 cm	+++	+
CO_2	10,600	Coupler and waveguide	RB	0.23 mm	+	+++
Argon	516	Quartz fiber	RB/FB	1.0–2.0 mm	++	+
KTP	532	Quartz fiber	RB/FB	1.0 mm	++	+
Nd:YAP	1,340	Quartz fiber	RB/FB		++++	+

KTP potassium titanyl phosphate, *Nd:YAG* neodymium-doped yttrium aluminum garnet, *CO_2* carbon dioxide, *Nd:YAP* neodymium-doped yttrium aluminum perovskite, *RB* rigid bronchoscope, *FB* fiber-optic bronchoscope

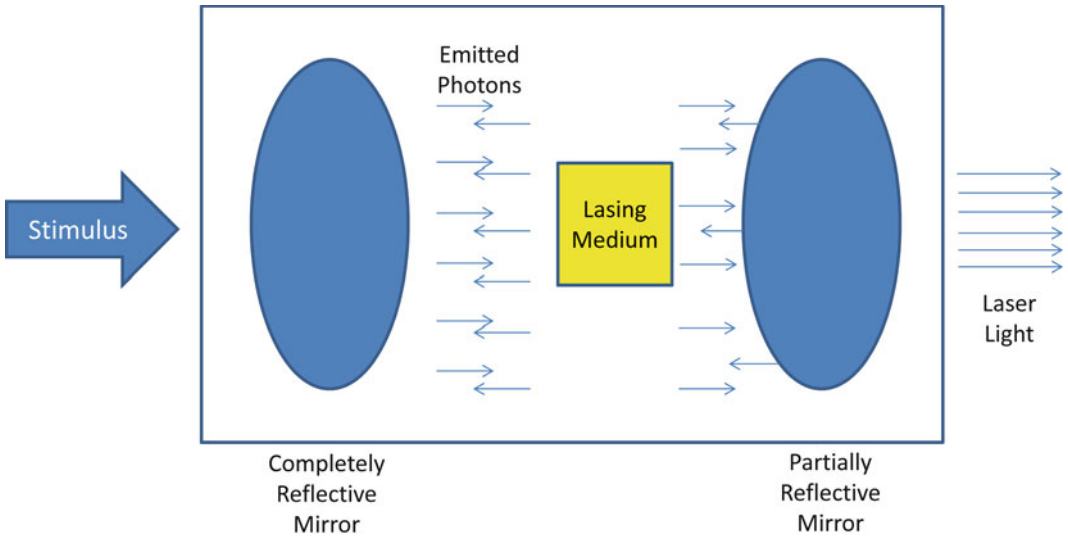

Fig. 35.1 Schematic of a theoretical laser system. As stimulus is applied through the lasing medium, exciting electrons which in turn release photons. These photons move in phase toward a partially reflective mirror. As some photons are reflected back through the lasing medium, there is amplification of the laser light that is generated. The resultant laser light emitted from the device is monochromatic, collimated, and coherent

bounce back and forth between the mirrors and through the medium, increasing numbers of excited electrons emit even more photons at the same wavelength and frequency. The percentage of coherent light emitted is an intrinsic property of the partially refractive mirror and varies between lasers.

Lasers can have thermal, photodynamic, and electromagnetic effects on the tissues they encounter, providing a tailored approach to the physical and clinical effects. Predominantly, laser bronchoscopy utilizes the thermal effects of light being transformed into heat as the laser interacts with living tissue. These effects are determined by the physical properties of the laser itself (i.e., wavelength) as well as the power density of the applied laser light. The power density (*power in watts/area of application x time of pulse s*) similarly determines the tissue–laser interaction. Lasers can be used for coagulation, leading to pale discoloration of the tissue associated with hemostatic effects. With more intense tissue interactions, carbonization occurs with blackish discoloration of the tissue and more robust destruction takes place. With even higher power densities, tissue vaporization can be achieved, although poor control of tissue effects ensues. Other forms of tissue destruction seen with medical laser use include photoablation, or removal of surface tissue or material, through thermal effects (i.e., CO_2 lasers) versus a mode of destruction termed photodecomposition as achieved with ultraviolet-emitting excimer lasers that have the benefit of better control of hemostasis. Obviously, the properties of the laser employed yield distinct effects. Therefore, the selection of the proper laser for a given desired effect requires an understanding of the particular laser–tissue interaction.

A tissue property defining a laser's ability to achieve hemostasis is related to the thermal relaxation time. The thermal relaxation time is the time by which a cylindrical structure (i.e., blood vessel) cools by diffusion. This is mathematically described by the following equation:

$$T_R\left(\text{thermal relaxation time}\right) = \text{radius}^2 / 4\alpha\left(\text{thermal diffusion of tissue} = 10^{-3}\text{cm}^2/\text{s}\right)$$

The importance of this equation is related to the operation of lasers used with intention of hemostasis. Essentially, if the pulse is longer than the cooling time, there will be a significant amount of heat that diffuses out of the target, and thus, destruction of surrounding tissues. Confined damage is best if laser pulse time is shorter than target cooling time.

Types of Lasers Used in Bronchoscopy

As previously stated, the particular characteristics of lasers are related to their lasing medium. In particular, the emitted wavelengths are discrete which determines the properties and their uses. Understanding of particular wavelength–tissue interaction is important in translation to clinical uses. Table 35.1 and Fig. 35.2 describe features of the different lasers used in airway interventions. Several features of the Nd:YAG (neodymium-doped yttrium aluminum garnet) laser make it ideal for use in the airway. With a wavelength of 1,060 nm, Nd:YAG lasers can be used through a flexible quartz fiber, which is a feature not available to the much longer wavelength CO_2 (10,600 nm) laser.

In the original description, utilizing laser for control of central airway disease made use of the CO_2 laser. Early in airway interventional laser therapy, this was used most often, but there are some difficulties inherent to this system. As the wavelength of CO_2 lasers is high, it cannot be passed through flexible quartz. Since the CO_2 laser is not "bendable," it requires use of a rather cumbersome articulating arm system with multiple mirrors with closed ventilation. It has uses in central airway obstruction, but requires rigid bronchoscopy and is not able to reach upper lobe disease and can be difficult to aim depending on anatomy. Recently, a photonic bandgap fiber has been developed for use with a CO_2 laser; however, experience with this system is limited at this time. The CO_2 laser has applications as a precision cutting tool with visible penetration that can be predictable based on power density. This technique can help control vessels up to 0.5 mm. Systems for CO_2 lasers utilize an articulating arm-mirror system with closed ventilation. It is most often used in conjunction with general anesthesia and rigid bronchoscopy. The lasing medium in CO_2 lasers is a mixture of CO_2, helium, and nitrogen. Most are equipped with a low-power red helium–neon aiming laser. Typically, the CO_2 laser is used with a power output of 10–15 W with a pulse duration of 0.5–1 s.

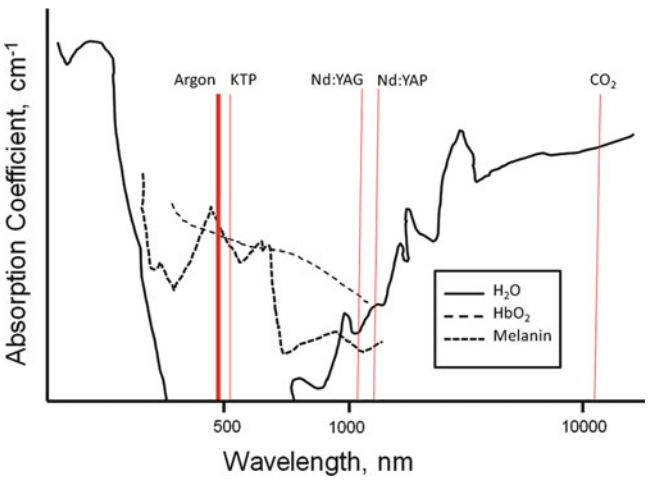

Fig. 35.2 Absorption coefficients for water, oxyhemoglobin, and melanin throughout the spectrum of medical lasers. The most frequently used medical laser wavelengths are indicated

The Nd:YAG (neodymium-doped yttrium aluminum garnet) laser with a wavelength of 1,060 nm can be passed through flexible quartz fibers. This laser utilizes an yttrium–garnet glass coated with neodymium. This laser has poor affinity for hemoglobin and water; therefore, it has deeper penetration and is more efficient for coagulation. Due to the scattering of laser energy associated with the Nd:YAG, the volume of adjacent tissue affected is determined by the power settings and the duration of firing. Carbonization and vaporization can be accomplished with higher power settings. This type of laser is good for much larger vessels up to 0.5 cm in diameter. Dark color (blue or black) increases absorption, and light surface colors enhance penetration. The *power density* (wattage per unit area) is below the surface of tissue and depends on color of the surface. The Nd:YAG laser in contrast to the CO_2 laser functions more as a radiator with volumetric heating with better absorption in dark tissues. This type of laser is applied through the use of a flexible quartz system with variable quartz fibers (ranging from 1.9 to 2.4 mm). Fibers may be cooled through continuous jet of air or CO_2 gas, but modern fibers may be used without cooling. With the Nd:YAG laser, there is a divergence of less than 10 ° with working distance of 5–10 mm between fiber tip and target area. This type of laser has better "tip control" through the use of the flexible fiber, thus upper airway treatments are possible as is steering. The downside of this control is a less predictable depth of penetration.

Argon lasers with a wavelength of 516 nm (blue green in visible spectrum) can similarly be used through a flexible quartz fiber, but suffers from much lower power; therefore, it is less useful for significant obstructing airway lesions. As it is highly absorbed by hemoglobin, its depth of penetration is attenuated, limiting its use for debulking airway masses; however, this leads to uses in airway coagulation

which is outside the scope of this chapter and will be discussed elsewhere. There are other lasers that have been applied to airway therapeutics including combination lasers such as the CO_2:Nd:YAG, KTP (potassium titanyl phosphate) lasers, holmium:YAG laser, and the Nd:YAP (neodymium-doped yttrium aluminum perovskite) laser, but limited experience with these platforms in airway therapies exists.

Notable Issues and Modifiers of Lasers

As many lasers are not in the visible light spectrum, coaxial lasers with visible light (i.e., HeNe laser) can be utilized to help aim these devices.

Some laser systems require cooling. Coaxial flow of air (or nitrogen or CO_2) has been used as a cooling source and to keep the laser tip clean. There are also internal (more mobile) or external (greater power at continuous exposure settings) water cooling sources for thermal control of lasers. A possible benefit of gas coolant systems is that they provide better visibility than fluid systems. Coolant systems can offer further safeguards through monitoring flow. If it is diminished by obstruction, controls can provide a safety measure to keep laser from firing. Inadequate flow leads to charring and fracturing of probes from fiber tip in contact probes. Modern fibers used with the Nd:YAG laser are often employed without the use of cooling systems.

Contact probes are an adjunct to laser therapies that provide tactile feedback to the operator and allow for decreased power through the use of direct contact of the laser through artificial sapphire crystal tips that are in direct contact with the tissue of interest. The tissue effects are augmented by direct contact, thus thermal gradients and power densities achieve therapeutic effects with lower overall power. The greater efficiency of energy utilization and greater control are potentially beneficial; however, cooling is required to decrease thermal damage to surrounding tissues, and visibility can be limited by close contact.

Type of Scope

Although there is an ability to use particular medical lasers through a flexible bronchoscope, utilization of rigid systems provide more secure control and immediate ability to intervene in the setting of potentially life-threatening complications. Significant debate has ensued surrounding the most appropriate scope to be used. Advantages of rigid systems include superior airway control, ease of removal of necrotic tissue, ease of ventilation, ability to tamponade areas of hemorrhage, improved visibility, and shorter operation time. Ventilation during intervention (out of the scope of this chapter) can be controlled better through rigid systems, and this approach provides larger visibility through greater working space. In the setting of high-grade lesions with a high propensity to bleed, a rigid system offers a greater ability to achieve hemostasis with preserved visibility. Also, flash fires have been reported much less frequently with rigid systems than with flexible scope use. Flexible systems do offer an ability to reach some distal lesions that are not approachable through rigid systems as well as a potential to "steer" the fiber tip with finer control. That being said, the use of combined flexible scopes when needed to reach distal disease through a rigid scope-secured airway offers the operator the most robust control. Appropriate uses of flexible systems include granulation tissue, distal disease, and nonobstructing lesions with the need for photocoagulation related to recurrent hemoptysis or in conjunction with a rigid intubation, namely, processes which are more readily controllable. At the present time, the overwhelming consensus is to perform laser airway therapy under general anesthesia with the use of rigid instrumentation if at all possible.

Indications, Contraindications, and Complications of Laser Bronchoscopy

The indication for laser airway therapy can be distilled to a simple concept, namely, to reduce airway obstruction to improve airflow and thus improve ventilation or palliate symptoms. Symptoms associated with obstruction are typically dyspnea, but cough, postobstructive infections, and hemoptysis are not infrequently encountered. The specific mechanism of obstruction can be quite varied and divided into malignant and nonmalignant processes. The term "benign" is often used to describe a non-neoplastic process; however, the course for many of these patients is far from benign. There are case reports and series describing laser use for nearly every potential cause of central airway obstruction from cancer as well as several processes that compromise airway lumen (Table 35.2). The types of lesions that are most amenable to laser intervention included polypoid endobronchial tumors with minimal submucosal infiltration or external compression. Table 35.3 outlines characteristics of airway lesions amenable to laser intervention.

Benign Uses

Ideally, there should be precise laser–tissue interactions through noncontact modes with adequate hemostasis. These are typically located in the subglottic larynx and trachea. CO_2 lasers with very controlled depth of penetration, precise tissue interactions, and very little scatter are ideal. The relative inability to use them through fiber-optic systems however can be limiting. Also, due to the hypovascular nature of webs, scars, amyloid deposits, hemangiomas, and papillomas, the CO_2 laser that does not require pigment for absorption can be useful.

Table 35.2 Indications for laser therapy in airway disease

Benign conditions	Malignant conditions	
Subglottic and tracheal stenosis	Cauterization of hemorrhage	
Endobronchial granuloma	Adenocarcinoma	
Broncholiths	Squamous cell carcinoma	
Benign tumors/hamartomas	Bronchogenic carcinoma	
Endobronchial inflammatory polyps	Carcinoid tumor	
Endobronchial amyloidosis	Large-cell carcinoma	
Tracheoesophageal fistulae	Small-cell carcinoma	
Hemangiomas	Tumors metastatic to the airway:	
Granulation tissue at transplant anastamosis	Thyroid	Thymus
Tubercular bronchial stenosis	Colon	Uterus
Dysplasia	Kidney	Testis
Bronchial stenosis after sleeve resection	Esophagus	Bone
Foreign body removal:	Melanoma	Larynx
Retained sutures	Breast	Liver
Tissue-embedded foreign bodies	Ovary	

Table 35.3 General characteristics of malignant lesions amenable to laser therapy and descriptions of favorable and unfavorable lesions

Tumor is not responsive to other reasonable therapeutic interventions	
Tumor should protrude into the airway lumen without obvious extension beyond cartilage	
Tumor length is small (<4 cm)	
The lumen is visible	
There is functional lung parenchyma distal to obstruction	
The symptoms of are predominately respiratory	
Favorable lesions	*Unfavorable lesions*
Polypoid, pedunculated	External compression causing obstruction
Large endobronchial component	Long, tapering obstruction
Distal lumen visible	Extensive submucosal disease
Lesion confined to trachea and mainstem bronchi	Total obstruction
Short lesion length (<4 cm)	Upper lobe and segmental lesions
Functional lung distal to obstruction	Chronic collapse
Short duration of distal collapse	Longer duration of distal collapse

Also, there are less collateral effects. Treatment of stenosis of the subglottic region is typically more favorable than tracheal lesions, but both typically require repeated treatments. The Nd:YAG laser is often employed in benign conditions obstructing the airway at lower power settings with positive effects.

Malignant Uses

Nd:YAG lasers have characteristics beneficial to use in malignant central airway-obstructing lesions. The depth of penetration permits coagulation of vessels that are several millimeters in diameter. The laser causes thermal destruction of tumor cells as well as vaporization. Debulking of large lesions is possible with coincident coagulation which is vitally important due to hemorrhage developing from tumor necrosis and perforation of large vessels. Indications for treatment of distal airway disease include obstructive pneumonitis and recurrent or persistent hemoptysis.

Table 35.4 Complications of laser airway therapy

Hemorrhage	Infection
Perforation of major vessel	Retinal damage
Endobronchial ignition	Respiratory complications
Pneumothorax	Cardiovascular complications
Pneumomediastinum	Atelectasis
Central air embolism	Breakage of contact probe tip
Laser plume	

Contraindications

The most important contraindication to laser bronchoscopy is the absence of an adequately trained operator. The technique can be performed very safely with significant efficacy in the well-trained operator's hands; however, without appropriate knowledge of the technique, disastrous consequences may be realized. From an anatomical standpoint, a few specific attributes of the airway obstruction may yield laser airway therapy ineffective with one exception. There is no role for medical lasers in the treatment of lesions causing external compression of the central airways (i.e., bulky mediastinal tumor, mediastinal fibrosis). Extensive airway involvement of bulky tumors or locations providing aiming difficulty prevents successful application. Total luminal obstruction without visualization of distal airway and upper lobe disease are relative contraindications due to risk for perforation secondary to uncertain direction of distal airways. In the setting of profound or refractory hypoxemia, unstable cardiovascular status, or coagulopathy, operator discretion is advisable.

Complications of Laser Airway Interventions

Overall, complications of laser airway treatments are uncommon in the well-trained hand, but significant issues may result from improper pretreatment assessments of anatomical boundaries, failure to control the airway, inadequate visibility, or failure to control the surrounding environment (Table 35.4). Most commonly, respiratory compromise is encountered due to hemorrhage or destroyed tissue in the airway or anesthesia effects. Patients may experience rapid changes in P_aO_2 and P_aCO_2 with the limitations in FiO_2 required for firing and suctioning and decreased airway luminal area due to instrumentation. Appropriate continuous monitoring is paramount to patient safety. Subsequent car-

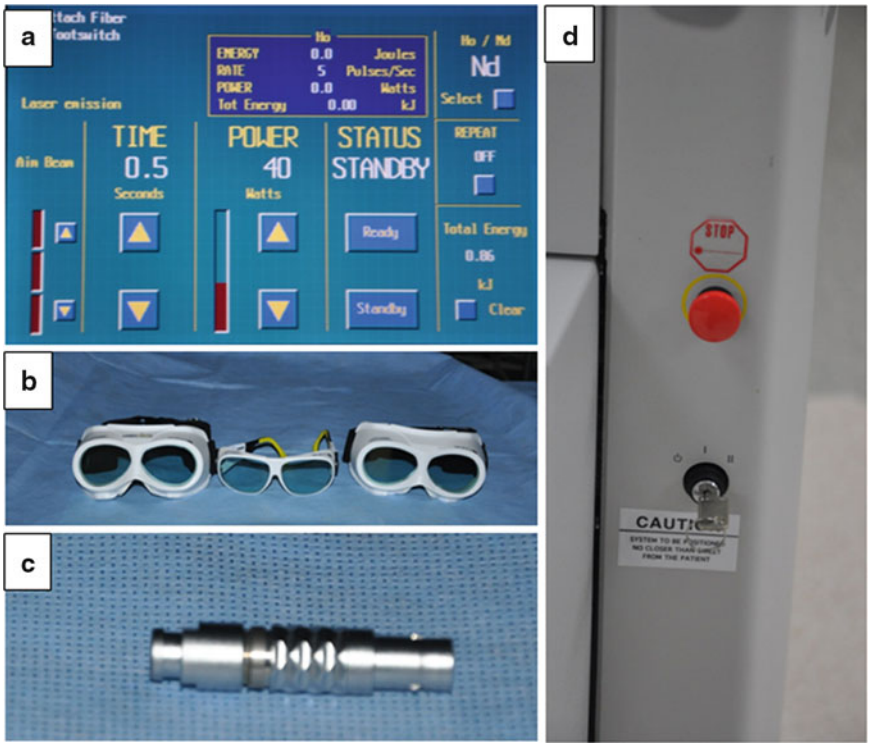

Fig. 35.3 Safety equipment for laser therapy application. Panel (**a**) depicts a typical control panel for a YAG laser system with readily visible power and pulse time. (**b**) shows protective eyewear for both patients and providers in the treatment area to prevent retinal damage. (**c**) is an interlock key for the laser system. If this key is not in place, the laser cannot be fired. (**d**) is the rear of the machine with lock and emergency stop control

diovascular compromise is possible and accounts for most of the laser therapy-associated mortalities.

Massive hemorrhage (>250 cc) has been reported in less than 5 % of laser applications (Table 35.5). Care should be taken to keep the lens clear and the field dry. Coagulation should be performed circumferentially from outside to inside. Appropriate choice in scope for given situations is vital. Massive hemorrhage may be prompted through perforation of major vessels either as a direct effect of tissue destruction into surrounding vessels or delayed from tumor necrosis. This is more common with an inability to visualize depth of penetration. At higher power levels (>40–50 W) or pulse times greater than 1 s, there is an unpredictable depth of penetration increasing risk of perforation. Although infrequent, endobronchial fires due to ignition of endotracheal tubes, fiber-optic scopes, suction catheters, and airway stents are possible and remain one of the most feared complications of airway laser applications. The risk increases at power levels greater than 50 W and FiO_2 greater than 50 %. Covered nitinol stents can be damaged at very low power densities. Moreover, ignition and damage of silicone and uncovered nitinol stents are possible with higher oxygen levels, blood covering the stent, and high power density levels. Consideration for removal of airway stents before laser applications should be employed if possible to minimize risks. Granulation tissue formation and bronchial stenosis have been reported as sequelae of endobronchial fires. Central air embolism has been reported as a complication of laser airway therapy possibly related to the use of contact probes and air coolant systems at high flows and in some cases resolves by decreasing flows. Avoidance of contact probes and minimizing airflow in coolant systems (0.8 L/s better than 1.5 L/s) is recommended. The postulated mechanisms suggest that direct air flows from the coolant sheath into open pulmonary venous tributaries, or alternatively, occlusion of proximal bronchus leads to increased distal pressures forcing gas into compromised vascular channels, although air embolism has been reported in patients without the use of air coolant systems. Other complications include infection or atelectasis from retained secretions or tissue and breakage of contact probe tips.

Operator specific risks include retinal damage and effects of laser plume; therefore, appropriate protection including wavelength-specific eye protection is advisable for everyone in the room along with protective covering of windows in surgical suite or endoscopy room. There are also interlock devices that will prohibit firing of the laser unless in place for activation (Fig. 35.3).

Table 35.5 Summary of severe complications associated with laser airway therapy. Includes 18 studies from 1982 to 2009

	Occurrences	Total patients		Total treatments	
Severe complications	N	N	(%)	N	(%)
Death	59	6,214	0.95	10,120	0.58
Hemorrhage (>250 cc)	113	5,923	1.91	9,692	1.17
Respiratory complications	132	6,000	2.20	9,882	1.34

Table 35.6 Summary of experienced operator-recommended techniques for airway Nd:YAG laser application

Pre-procedure recommendations
Study anatomy with imaging before the procedure; identify extent and margins of lesion(s) and surrounding vasculature
Patient and scope selection in advance
Use of rigid scope for high tracheal and highly vascular lesions to control airway and hemorrhage
Use flexible scope for peripheral and low-grade lesions only
Suggest general anesthesia if at all possible
Ensure appropriate patient monitoring throughout the procedure
Procedural recommendations
Keep FiO2 as low as possible during firing (<50 %)
Confirm that cooling systems are working properly
Palpation of the tumor or stenosis with the scope
Maximize distance from tumor to endotracheal tube
Maintain laser fiber at least 5 mm from distal end of scope and 5 mm from mass/lesion for firing
Fire laser parallel to airway to minimize risk of perforation
Begin with low power (40–70 W) and increase for desired effect:
Coagulation – long, low power versus resection – short, high power volleys
Duration of firing ~0.5 s in duration, volleys 2 s apart, 25–30 maximum pulses
Keep laser tip clear of carbon residue which could ignite
Contact probe used when 70 W not successful (5 W at 0.4 s)
Mechanical removal of material to decrease procedure time
Post-procedural recommendations
Appropriate postoperative monitoring with trained personnel

Techniques of Laser Use in the Airway

Several independent centers with vast clinical experience have cited their recommendations regarding the techniques that they employ for laser use in the airway (Table 35.6). Although these suggestions come from experienced operators, personal experience with the lasers is paramount to understanding the true power of their use. Preliminary procedures including adequate imaging to characterize the location and extent of the lesion of interest are of utmost importance in planning. Through proper review of imaging, direction and location of major vessels surrounding the laser field can be mapped. Appropriate control of the patient is best achieved with general anesthesia with comprehensive monitoring. Once in the airway with the laser, minimizing the fractional inspired oxygen (FiO_2) concentration is necessary with a goal to maintain it below 50 %. Power setting for Nd:YAG lasers range from 20 to 100 W in the literature with the vast majority being in the midrange. The pulse times typically employed last from 0.2 to almost 2 s depending on the application, but the median is in the 0.4–0.5-s range. Typically, a volley of pulses in a given location, working distally or circumferentially from the outside inward, achieves the most thorough tissue destruction while maintaining control of hemostasis and a clear view of the work area. Although rigid scopes provide ideal control, in the setting of a flexible scope approach, maintaining a maximal distance from the endotracheal tube is paramount. Moreover, the tip of the fiber needs to be at least 0.5 cm from the tip of the bronchoscope in flexible systems to diminish risks of ignition or scope damage. Similarly, the tip of the laser fiber is best maintained approximately 0.5 cm from the area of interest for optimal aiming control. If greater power is needed, contact probes can be used to decrease overall power needs, but generate greater tissue destruction through direct contact. Care should be taken to start with lower power and increase as needed for the desired tissue effects. The tip of the fiber must also remain clear from debris for effective use and to decrease ignition risks. After tissue destruction is achieved through either contact or noncontact modes, excision can be accomplished with the use of forceps, snares, baskets, scissor tools, and/or the scope itself. Upon completion of the laser treatment and control of procedural bleeding and patient cardiopulmonary status, it is essential to recover the patient in an appropriate monitored setting with adequately trained personnel.

Outcomes of Laser Treatments

The gestalt from the previously reported large series is that the best outcomes are seen in slow-growing, proximal disease, and worst outcomes are noted in upper lobe disease or combined intrinsic/extrinsic disease. For benign processes, significant improvements in symptoms can be achieved through the use of laser therapy, although repeated interventions are the norm. Symptom palliation including improvement in dyspnea, cough, and hemoptysis is achievable in more than 75 % of patients receiving laser therapy for airway obstruction in malignant disease, although the characteristics of the lesions influence these outcomes significantly. In the early studies by Dumon, favorable outcomes were achieved in most. From the Cleveland Clinic experience, more than 90 % of patients received either excellent or good responses as measured by symptom improvement and objective measures. Along with improvements in symptoms, spirometric, performance status, and imaging improvements can be achieved with proper patient selection. Outcomes have correlated with the location of obstruction significantly, with laser therapy treatment of more central lesions yielding higher response rates than upper lobe disease.

Although laser therapy for malignant disease is employed for palliation of symptoms, comment on increasing longevity in patients receiving this therapy is warranted. In the absence of randomized or controlled trials of airway laser interventions, comparisons of mortality have been based on

Table 35.7 Dumon's 10 commandments of safe YAG laser resection

1.	Know the anatomical danger zones: aortic arch, pulmonary artery, and esophagus being the main hazard areas
2.	Have a well-trained laser team, including an anesthetist specialized in light general anesthesia and two assistants drilled in emergency response procedures
3.	Screen patients carefully: any endoluminal growth is amenable to laser resection, but purely external compression is beyond the reach of the technique
4.	Use the rigid bronchoscope technique (custom-made open tube, light general anesthesia, straight telescope, and two suction catheters) for any high-grade obstruction, especially if malignancy is involved
5.	Monitor blood gases and cardiac performance. At the least sign of hypoxemia, interrupt treatment long enough to oxygenate the patient, if necessary under closed circuit conditions
6.	Fire the laser parallel to the wall of the airway; never aim directly into it
7.	Coagulate at will, but avoid using the laser at high power settings; mechanical resection after laser coagulation is preferable to laser resection alone whenever possible
8.	Do no neglect hemorrhage, for even slow bleeding will lead to hypoxemia if left untreated
9.	Terminate each procedure with a thorough laser irradiation of the resected area and a tracheobronchial toilet to remove all secretions and/or debris
10.	Keep the patient under observation in a specially outfitted recovery room for a reasonable period of time

historic controls that were untreated or treated with external beam radiation and/or chemotherapy. Moreover, most malignancies are treated with multiple modalities. Combination therapies have included both radiation approaches as well as chemotherapy, with the latter being utilized more frequently. Desai and coworkers compared outcomes of patients treated with external beam radiation with combined Nd:YAG with historic radiation recipients and found a mortality benefit for combined modality (150 vs. 267 days, $p=0.04$) in those requiring emergent intervention. The addition of brachytherapy to Nd:YAG treatment demonstrated improved longevity of the therapeutic effect (mean 16.4 ± 2.5 vs. 40.8 ± 9.4 weeks, $p=0.001$) with the dual modality. Moreover, there was a benefit when photodynamic therapy was used after Nd:YAG treatment in patients with airway obstruction in malignancy. In one study of outcomes related to Nd:YAG therapy, patients with greater than 75 % restoration of airway lumen and those either pre- or post-treated with external beam radiation had improvements in longevity particularly in squamous cell type. Even in the setting of respiratory failure requiring mechanical ventilation, outcomes including successful extubation and prolonged longevity have been seen in patients after use of Nd:YAG lasers for malignant central airway obstruction. Success in this setting again favored intrinsic obstruction, suggesting the need for appropriate preoperative assessment. In a retrospective comparison of Nd:YAG therapy alone or in conjunction with other modalities, there was improvement in the median time for second intervention by 1.7 months ($p=0.002$ compared to YAG alone) and in survival that was prolonged by 4.9 months ($p<0.001$) in non-small-cell lung cancer and 3.2 months in all forms of cancer ($p=0.002$). For particular malignant cell types (i.e., carcinoid), Nd:YAG therapy has been used with curative intent with good success.

Conclusions

In the right hands and in the right situation, laser therapy for the relief of airway obstruction is an incredibly powerful tool. As an adjunct to other interventional techniques, laser therapy bolsters the armamentarium of its operator to deal with dire situations. Paramount to its successful application is an understanding of the limitations of the technique and safeguards for the patients receiving this treatment. Although written by Jean-François Dumon more than 25 years ago (Dumon 1985 YAG Surgery Book), an appropriate and poignant summation of keys to successful laser airway therapy can be found in the 10 Commandments (Table 35.7). These tenants remain the core of the use of medical lasers for airway disease.

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Brachytherapy

36

Maher Tabba

Introduction

Lung cancer causes more deaths in the USA for both men and women than any other type of cancer. The most recent statistics that are available from 2006 reveal that the number of deaths due to lung cancer exceeded the combined deaths due to breast cancer and prostate cancer. Non-small cell lung cancer (NSCLC) usually accounts for almost 80% of the lung malignancies. Unfortunately, less than 20% of these patients undergo surgical resection as the majority of them are usually in an advanced stage at the time they present for diagnosis and treatment. However, lobectomy is still the definitive treatment for early stage NSCLC of the lung. Lobectomy decreases the rate of recurrence and the rate of developing a second malignancy, while improving the rate of survival. More than 90% of patients with early stage lung cancer undergo surgical resection, with 10% of these patients also requiring postoperative treatment with chemotherapy, radiation therapy, or a combination protocol.

Radiation therapy has long been used to treat patients with lung cancer in combination with chemotherapy and/or surgery. It also may be used as the sole therapy. There are two major radiation therapy modalities available in treating lung malignancy:

1. External beam radiation therapy (EBRT): Radiotherapy is applied on the target thoracic or mediastinal area. The major indications are as follows:
   - Before surgery to decrease the size of the original tumor and to make the surgical resection more successful
   - After surgery for locally advanced stage (positive margin)
   - Nonoperable advanced stage
   - Nonoperable patients with early stage
   - Nonoperable patients with recurrent malignancy
   - Palliation in patients who develop a partial lung collapse or hemoptysis
2. Local radiation therapy or brachytherapy: Radiation treatment is applied locally and close to the tumor area. This radiotherapy modality has been used to treat a variety of malignancies, such as brain, eye, head and neck, breast, lung, gastrointestinal, genitourinary, and soft tissues.

This chapter will focus on endobronchial brachytherapy (EBB) as a useful localized radiation therapy modality in patients with symptomatic malignant endobronchial lesions. The benefits of EBB will be discussed with particular attention to high-rate dosage, which is becoming the most frequently used brachytherapy treatment option.

History

Brachytherapy is derived from the Greek word "brachios," which means short distance, and is also known as internal radiotherapy, sealed source radiotherapy, curietherapy, or endocurietherapy. It is a form of radiotherapy where the radiation source is placed inside or adjacent to the area requiring treatment. Robert Abbe (1851–1928), a pioneer American surgeon and radiologist, is considered the founder of radiation oncology. Together with his colleagues Pierre and Marie Curie, he pioneered the medical uses of radiation. He introduced the practice of using radiation in treating cancers at St. Luke's Hospital of New York in 1905 by placing removable radium source tubes into tumor beds. In 1922, Yankauer treated two patients with endobronchial malignant lesions by bronchoscopic placement of encapsulated radium sources. The advance of using flexible bronchoscopy assisted in making this method of treatment more feasible.

William Myers (1908–1988), a pioneer in nuclear medicine at Ohio State University College of Medicine, developed multiple radioisotopes (i.e., gold-198, cobalt-60, iodine-125, and phosphorus-32) for clinical brachytherapy use. In 1960,

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Henschke first introduced the afterloading technique. This technique consists of implanting a thin tube (afterloader) to the targeted tissue area and placing the radioactive source remotely in the tube. Additionally, this technique helped in minimizing the radiation exposure for staff. Engineered radionuclide wires (tantalum 182 and iridium-192) with thin and flexible properties made this technique more viable. Cutting these wires to any length became much easier while simultaneously decreasing the level of implantation discomfort for patients. Recently, with the advance in the new imaging technologies including the PET scan, CT scan, and the MRI, it is possible to achieve more precise therapeutic positional accuracy. Thus, these imaging advances have given rise to a heightened interest in brachytherapy.

Types of Thoracic Brachytherapy

There are three types of brachytherapy that may be used in treating lung cancer:

1. Intraluminal or endobronchial brachytherapy (EBB): The radioactive source is placed in a space near to airway tumor (within 5–10 mm).
2. Interstitial brachytherapy: The radioactive source is placed directly into the targeted lung tissue.
3. Image-guided brachytherapy therapy (IGBT): The radiation therapy is delivered by using imaging technologies to create multiple three-dimensional images of the targeted tissue. This technology, "BrachyVision," also has the ability to coregister multiple 3D image data sets by using computerized tomography, magnetic resonance, positron emission tomography, and ultrasound. The targeted tissues can be easily navigated by the rotating tools to deliver an optimal therapy and spare the normal tissue.

Further, there are three types of radiotherapy that may be delivered:

(a) Low-dose rate (LDR)
(b) High-dose rate (HDR)
(c) Pulse dose rate (PDR).

Low-Dose Rate (LDR) and High-Dose Rate (HDR)

Delivering LDR or HDR is achieved by placing a protected radioactive source directly within the tumor via radioactive plaques, needles, tubes, wires, or small "seeds" made of radionuclides. These radioactive materials are placed over the surface of the tumor or implanted within the tumor or may be placed within a body cavity, such as an airway, surrounded by the tumor. Multiple isotopes have been used, but iridium-192 is the most commonly used isotope.

Low-dose rate (LDR) brachytherapy involves placing the radioactive materials (i.e., dose rate less than 1–2 Gy, per hour) inside the body for extended periods of time. The American Brachytherapy Society (ABS) suggests administering 30 Gy at 1.0 cm if brachytherapy is the sole treatment for palliation. A total dose of 20 Gy is recommended if the brachytherapy is used in combination with EBRT. Patients are usually admitted to the hospital for few days to complete the full course of treatment and placed in a special room with radiation precaution measures. The overall symptomatic improvement (dyspnea, chest pain, and hemoptysis) in using LDR is 53–92%.

High-dose rate (HDR) brachytherapy involves using high-energy radiation (i.e., dose rate greater than 10–12 Gy per hour). The American Brachytherapy Society suggests multiple therapy regimens when the HDR is used as sole treatment for palliation: 3 weekly fractions of 7.5 Gy each, two fractions of 10 Gy each, or four fractions of 6 Gy each (all prescribed at 1.0 cm). When HDR is used in combination with EBRT, two fractions of 7.5 Gy each, three fractions of 5 Gy each, or four fractions of 4 Gy each are recommended. The interval between fractions is generally 1–2 weeks. This is an outpatient procedure performed by delivering the brachytherapy dose within a just few minutes via inserting and then removing the radioactive beads, with the total radiation dose at the end of the sessions ranging between 500 and 4,000 Gy.

Moreover, placing a metallic stent at the site of the malignant lesion after completing HDR treatment has improved local control. Overall, HDR has demonstrated significant symptomatic improvement in dyspnea, cough, hemoptysis, and postobstructive pneumonia in treated patients. Side effects are less than 10%, and in comparison to LDR, HDR has significantly shortened the treatment time, minimized the need for hospitalization and associated costs, as well as decreased catheter dislodgment.

Pulse dose rate (PDR) is a brachytherapy modality that combines the physical advantages of high-dose-rate (HDR) brachytherapy such as isodose optimization and radiation safety with the radiobiological advantages of low-dose-rate (LDR) brachytherapy. The radiation is delivered in a series of short exposures of 10–30-min intervals each hour to approximate the same total dose overall as with the LDR. However, it is not commonly used in the USA.

Applications

Thoracic brachytherapy is used for both lung malignancies and mesothelioma. In particular, for lung malignancies, it is useful across multiple disease statuses: endobronchial disease, early stage disease, and locally advanced disease.

Interstitial Brachytherapy

Applications of the thoracic brachytherapy have been used widely in the following conditions:

(A) Early Stage Disease: Lobectomy is still the standard of therapy for patients with early stage non-small cell cancer (NSCC) of the lungs. Segmentectomy and wedge resection are two alternative surgical treatments for patients who are unable to tolerate complete lobectomy. Sublobectomy is an acceptable treatment option for patients with poor cardiopulmonary function, poor performance status, advanced age, or comorbid medical conditions. The local relapse is 50% with wedge resection, 22.7% with segmentectomy, and 4.9% with lobectomy. Recurrence occurs secondary to the lymphatic vessels invasion. This involvement usually correlates with the initial tumor size. Tumors that are less than 1 cm in size have 25% lymphatic invasion in comparison to tumors larger than 3 cm that have 52% lymphatic invasion. Adding local brachytherapy for incomplete surgical resection has resulted in improved outcomes in contrast to incomplete resection without brachytherapy.

(B) Locally Advanced Disease: The surgical resection of some lung cancers are challenging and limited because of the involvement in nearby anatomic organs such as the bones or major vessels. Maintaining a free margin (i.e., tumor plus a rim of normal tissue) after the partial resection cannot be always achieved. The preferred free margin is usually 1–2 cm. The absence of a free margin is associated with a higher degree of cancer recurrence. Further, about 7.8% of patients who undergo surgical resection for NSCC of the lung leave the operative room with a positive margin. Brachytherapy has been used in this scenario to treat the remaining unresected cancer tissue and to minimize the risk of recurrence. Brachytherapy after the sublobar resection is delivered via multiple methods: planar seeds implantation, intraoperative radiation, and afterloading brachytherapy catheter delivery. The type and the amount of the therapy are usually decided with close coordination between the surgeon and the radiation oncologist.

(C) Mesothelioma: Brachytherapy has been used in some centers to treat recurrence or metastatic mesothelioma, especially in patients who already received radiation therapy. Yet radiating the heart, esophagus, and spinal cord is usually a major concern.

Intraluminal or Endobronchial Brachytherapy (EBB)

Malignant recurrent endobronchial lesions are responsible for 60% of the mortality from postobstructive pneumonia, respiratory failure, and sepsis in patients with lung cancer. The goal of intraluminal brachytherapy is palliative, and it aims to control the growth of tumors and to achieve reduction in their sizes. Response to treatment usually occurs within a short period of time (i.e., 4–6 weeks).

Table 36.1 Speiser's symptomatic scoring index

Score	Hemoptysis
0	None
1	Less than twice per week
2	Less than once daily but greater than twice per week
3	Daily, bright red blood or clot
4	Decrease of Hg or Hct more than 10%, greater than 150 ml, requiring hospitalization or leading to respiratory distress
Dyspnea	
0	None
1	Dyspnea on moderate exertion
2	Dyspnea with normal activity, walking on ground level
3	Dyspnea at rest
4	Requires supplemental oxygen
Cough	
0	None
1	Intermittent, no medication necessary
2	Intermittent, nonnarcotic medication
3	Constant or requiring narcotic medication
4	Constant or requiring narcotic medication but without relief
Pneumonia or elevated temperature	
0	Normal temperature, no infiltrate, WBC < 10.000
1	Temperature >38.5 and infiltrate, WBC < 10.000
2	Temperature >38.5 and infiltrate and/or WBC > 10.000
3	Lobar consolidation on radiograph
4	Pneumonia or elevated temperature requiring hospitalization

Source: Celebioglu B, Gurkan OU, Erdogan S, Savas I, Köse K, Kurtman C, Gonullu U. High dose rate endobronchial brachytherapy effectively palliates symptoms due to inoperable lung cancer. Jpn J Clin Oncol. 2002;32(11):443–8 (Reprinted with permission)

Using EBB to treat endobronchial lesions substantially impacts patient outcomes by:

1. Improving respiratory symptoms such as dyspnea, cough, stridor, and hemoptysis
2. Improving lobe collapse and lung reexpansion
3. Improving ventilation and perfusion in the affected lobe
4. Improving exercise tolerance
5. Improving lung function parameters

In terms of treatment criteria, there are several factors that should be considered when evaluating patients for endobronchial brachytherapy. These factors are divided into two categories:

(A) Patient-Related Factors:

- Symptomatic endobronchial lesion: dyspnea, cough, lobe collapse, or postobstructive pneumonia. Speiser et al. suggest a symptomatic scoring index to evaluate the patient with endobronchial lesion before and after the therapy (Table 36.1)

- Failure of standard chemotherapy, EBRT or both
- Patient received maximum dose of EBRT or unable to tolerate the treatment
- Patient is able to tolerate bronchoscopy
- Adequate life expectancy (i.e., usually more than 3–5 months)

(B) Lesion-Related Factors:

- Biopsy-proven malignancy
- Accessibility to the catheter placement
- The lesion is endobronchially without extrinsic compression
- No significant ulceration
- No major vascular involvement

In terms of efficacy, clinical improvement has been reported in numerous series. In a study of 270 patients with advanced lung cancer and recurrent endobronchial lesions that underwent EBB treatment, significant symptomatic improvement was achieved in 80% of the patients with a 5-month median duration of palliative period. Symptomatic improvement response rates were as follows: dyspnea 76%, cough 77%, hemoptysis 92%, lung reaeration 73%, and postobstructive pneumonia 82%. It should be noted that gender, age, and histological type were not found to be predictive of brachytherapy success. Additionally, a survival benefit has been observed in patients undergoing EBB. In a study that included 81 patients with lung cancer who underwent chemotherapy and/or EBRT with persistent endobronchial lesion, a significant survival benefit was found in patients who underwent EBB in comparison with patients who did not (13 months versus 5 months).

Short-term efficacy has been documented by histological biopsy after EBB treatment. In a study of 106 patients with endobronchial lung cancer, who were treated previously with surgical resection, EBRT, or were not eligible for any therapy, underwent treatment with EBB. A complete histologic response was achieved in 60% at 3 months follow-up. The 3 and 5-year survivals were 47.4% and 24%, respectively. Factors significantly associated with treatment failure were high tumor volume (i.e., tumor length >2 cm), bronchial obstruction (i.e., more than >25% of the lumen), tumor visibility on CT scan, and previous endoscopic treatment.

Patients with central malignant lesions showed significant improvement of these symptoms in comparison to patients with peripheral malignant lesions.

EBB has been also used to treat roentgenographically occult endobronchial malignancies. Nineteen patients with limited endobronchial non-small cell lung carcinomas measuring less than 1 cm in diameter and not visible on a CT scan of the chest underwent EBB due to lack of other treatment options. Tumor control over a 2-month period was 83%, and over 1 and 2-year periods was 75% and 58%, respectively. Finally, complete cancer resolution was achieved in few case reports. Two patients with T1N0 squamous cell lung cancer and poor lung function to undergo surgical resection received EBB. A complete cancer resolution at 25 and 54-month follow-up was achieved.

Combination Therapy of EBRT and EBB

In general, external beam radiation therapy (EBRT) alone provides superior and more sustained palliation to patients than EBB alone, with fewer re-treatment sessions, as well as a modest gain in survival time. In patients with advanced inoperable lung cancer, combination therapy with EBRT and EBB has resulted in longer survival durations. However, these durations were not statistically significant in relationship to EBRT alone. This observation was noticed especially in squamous cell carcinoma. Respiratory symptoms (i.e., dyspnea, hemoptysis, cough, and chest pain) were not different between the two groups. Yet patients with atelectasis secondary to endobronchial lesion responded well to the combination therapy. Patients with roentgenographically occult lung cancer treated with combined EBRT and EBB achieved both a high remission rate and low recurrence.

EBB with Other Bronchoscopic Interventional Therapies

Combining EBB with other treatment modalities such as electrocautery, cryotherapy, and Nd-YAG laser therapy to treat inoperable or advanced lung cancers achieves a larger degree of local control of the endobronchial malignant lesions.

EBB and Photodynamic Therapy (PDT)

Brachytherapy can be combined with photodynamic therapy in patients who have nonoperable endobronchial malignancy, malignancy relapse, or tumor residual after PDT. In a series, 32 patients with non-small cell bronchogenic carcinoma and bulky endobronchial tumors were treated using a combination of PDT and brachytherapy. At a mean follow-up of 24 months, 26 patients were free of residual tumor and local recurrence.

EBB and Endobronchial Ultrasound Bronchoscopy (EBUS)

EBUS has been used for EBB treatment planning. It helps in evaluating the extension of the targeted endobronchial lesion, vascular involvement, or lymph-node metastasis, which escaped other images.

Techniques

Initial Evaluation

A flexible bronchoscopy should be performed in the beginning to evaluate the location and the character of the endobronchial lesion, such as the anatomic site and the location of the lesion in reference to a fixed landmark (carina), the length of the lesion, and the degree of the airway obstruction. Speiser and his colleagues proposed scoring criteria for the degree and location of the airway obstruction as displayed in Table 36.2. This information should be recorded for dose prescription purposes.

An adequate passage should be visible through the endobronchial lesion to pass the catheter. If the lesion is occluding the lumen, a passage should be created first by using mechanical debridement, laser, or electrocautery. This procedure should be done in a separate session prior to the brachytherapy treatment.

Table 36.2 Speiser's obstruction definitions and scoring criteria

Trachea	>50% = 10	<50% = 6	<10% = 2
Main bronchus	>50% = 6	<50% = 3	<10% = 1
Lobar bronchus	>50% = 2	<50% = 1	
Atelectasis	2 per lobe		
Pneumonia	2 per lobe		

Source: Celebioglu B, Gurkan OU, Erdogan S, Savas I, Köse K, Kurtman C, Gonullu U. High dose rate endobronchial brachytherapy effectively palliates symptoms due to inoperable lung cancer. Jpn J Clin Oncol. 2002 Nov;32(11):443–8 (Reprinted with permission)

In patients with early stage central lung malignancy, an adequate assessment with EBUS prior to EBB should be conducted for adequate staging. Lesions with cartilage invasion should be treated as stage IA and should undergo surgical evaluation. Lesions without cartilage involvement will be appropriate for any form of local therapy such as EBB, laser, or electrocautery therapy or mechanical removal.

Catheter Placement

A flexible polyethylene catheter is usually inserted into the airway by using a flexible bronchoscopy with adequate channel size for the catheter delivery. A transnasal approach is used when performing the bronchoscopy (Fig. 36.1). The majority of the cases can be done under conscious sedation, but general anesthesia may be needed in special circumstances. The distal end of the catheter is placed at the site of the endobronchial lesion, and it should be about 2 cm beyond the distal end of the lesion (Figs. 36.2 and 36.3). In the alternative, the catheter may also be placed by wedging the tip of the catheter into a segmental bronchus. This technique helps in minimizing any catheter displacement. It is important to note that the catheter should not be forced when resistance is felt. The bronchoscopy and the guidewire should be removed gently and the catheter marked at the site of its exit from the nostril and secured into position with adhesive tape. The position is verified with fluoroscopy and CXR. A second and third catheter may be placed in similar fashion to more fully surround the tumor.

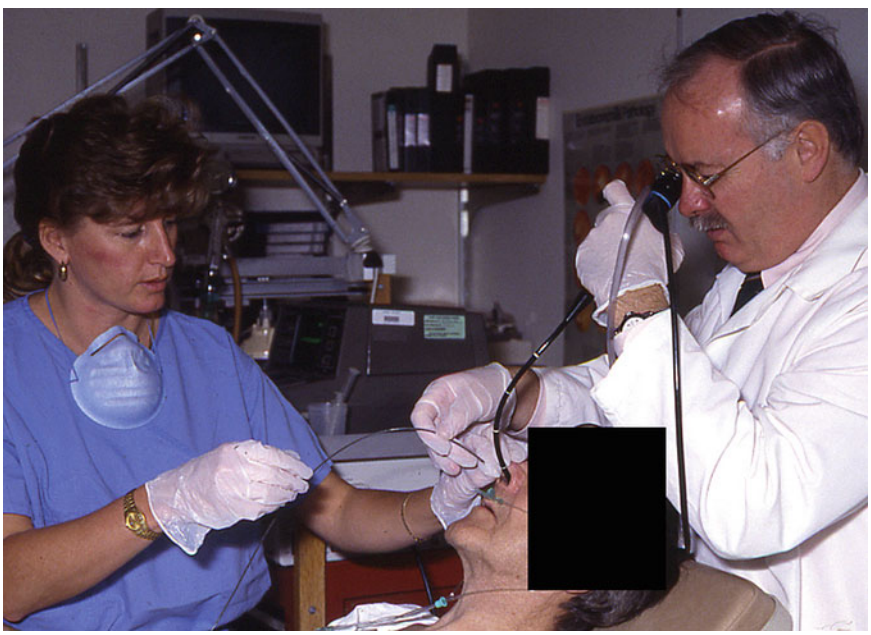

Fig. 36.1 Endobronchial brachytherapy catheter is being adjusted under the bronchoscopic guidance after the initial insertion (Courtesy of Lahey Clinic, Burlington, MA)

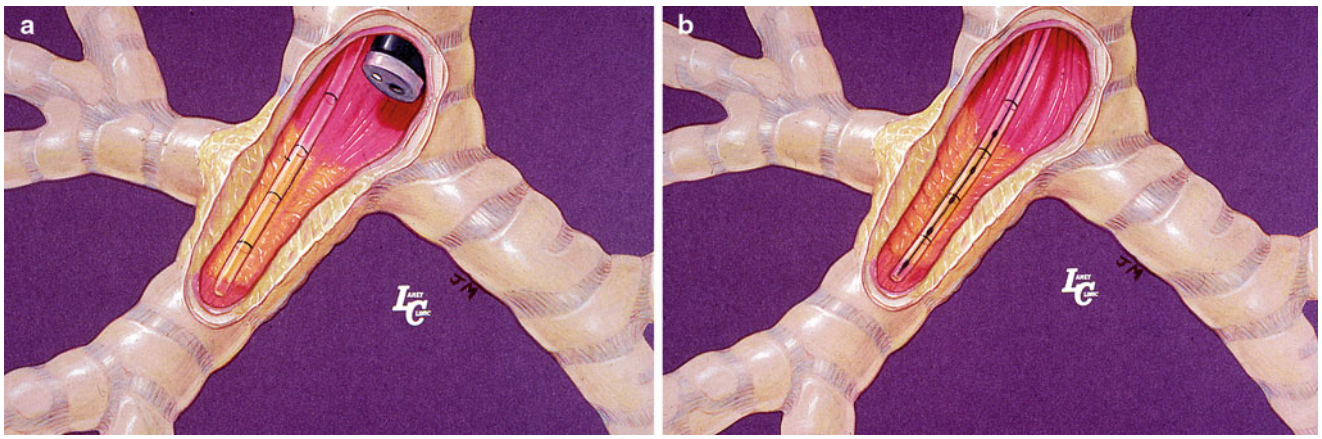

Fig. 36.2 (**a**) Verifying the brachytherapy catheter position in the airway next to the endobronchial lesion with bronchoscopy. (**b**) The brachytherapy catheter after loading the radioactive source (seeds) (Courtesy of Lahey Clinic, Burlington, MA)

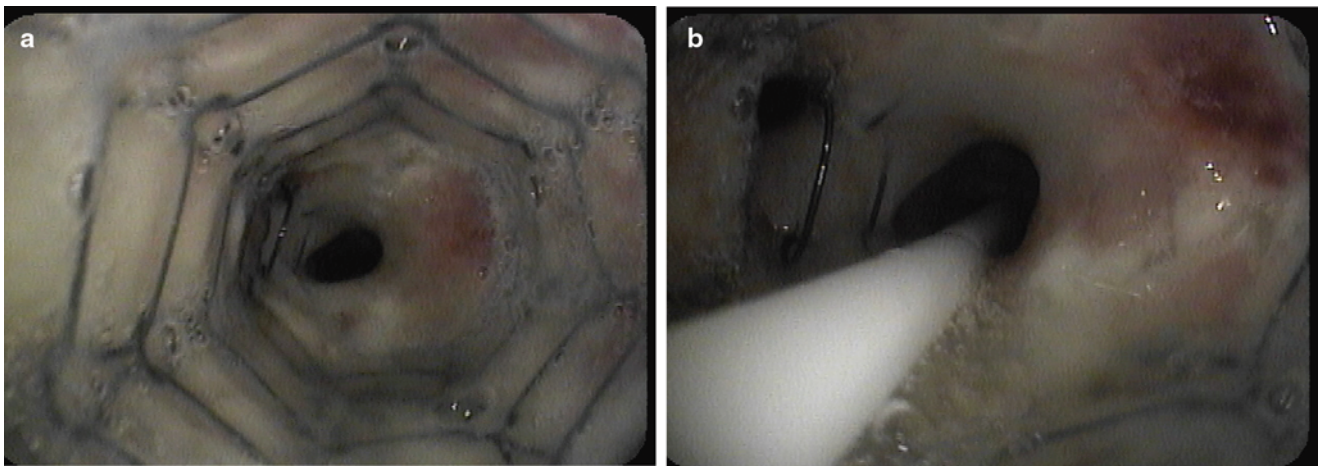

Fig. 36.3 (**a**) Malignant endobronchial stenosis at the distal end of the *left* main stem where the metallic stent was placed. (**b**) The endobronchial brachytherapy catheter is passed distally for about 2 cm beyond the stenosis (Courtesy of Lahey Clinic, Burlington, MA)

Treatment Planning

Nonradioactive ("dummy") sources are introduced into the catheter to the level of the bronchial obstruction. Radiographic verification is performed to geographically define the eventual position of the radioactive source. Different prescription points (i.e., total dose and number of fractions) have been used. In practice, prescription depths of 0.5–2 cm have been used by numerous investigators. The American Brachytherapy Society suggested two methods:

1. Prescribing the radiation dose to a fixed distance from the center of the catheter, which is typically 10 mm. This method is used when treating a lesion located in the trachea or major airways.
2. Prescribing the radiation dose at various distances from the center of the catheter(s), depending on the diameter of the airway. This method is used when treating lesions in smaller airways. It usually ranges between 5 and 10 mm, depending on the bronchus.

The treatment margin should include 1–2 cm at the proximal and distal end of the endobronchial lesion. With advanced technologies, three-dimensional brachytherapy treatment planning may provide more effective and accurate targeting of the tissue.

Treatment Session

The patient should be taken to the Department of Radiation Oncology for manual or remote loading of the radioactive source. Once the catheter is connected to the treatment unit, a calculated dose is delivered. After completing the treatment

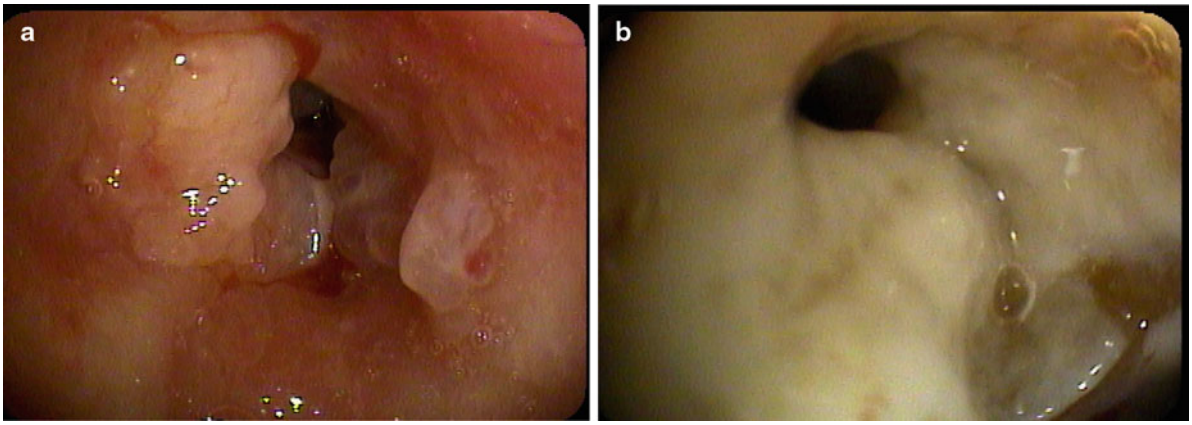

Fig. 36.4 (**a**) Malignant endobronchial lesion obstructing the *left upper* lobe. (**b**) Postbrachytherapy treatment with the pus draining from the postobstructing pneumonia in the same lobe after the resolution of the obstructing lesion (Courtesy of Lahey Clinic, Burlington, MA)

session, the catheter is disconnected from the treatment unit and removed (Fig. 36.4). Then, the patient may be discharged home with specific instructions to contact the treating physician if acute dyspnea, cough, or hemoptysis occurs. The American Brachytherapy Society suggests grading the bronchoscopic response to the treatment as excellent, good, fair, and poor.

Indications for EBB

The indications for endobronchial brachytherapy recommended by the American Brachytherapy Society are listed in Table 36.3.

Other proposed indications are as follows:

- Sole therapy for small-sized peripherally located lung cancer in nonoperable patients
- Sole therapy for localized bronchial carcinoma
- Small, central, and early lung carcinoma
- Central carcinoma in situ or precancerous lesions
- Benign endobronchial lesion or hypertrophic lesions after lung transplant

Contraindications

The following are contraindications for EBB:

1. Patient is unable to undergo bronchoscopy
2. Significant endobronchial ulceration at the site of the lesion
3. Airway fistula to the surrounding organs
4. The endobronchial lesion involves a major vascular structure
5. Complete obstruction of the airway by the tumor

However, in event of a complete airway obstruction by the tumor, a passage could potentially be created inside the lesion by using other bronchoscopic interventional techniques such as mechanical debridement, Nd:YAG laser, or electrocautery before the EBB is initiated.

Table 36.3 The American Brachytherapy Society recommendations for endobronchial brachytherapy

A – Symptomatic endobronchial malignant lesion associated with cough, dyspnea, hemoptysis, or postobstructive pneumonia
B – Patients who are unable to undergo surgery because of poor pulmonary function or metastasis
C – Patients who are unable to undergo EBRT because of poor pulmonary function or completed the maximum dose of EBRT
D – Tumors that protrude into the lumen are considered suitable, as opposed to extrinsic tumors that compress the bronchus
E – Patients with life expectancy more than 3 months

Complications

The most common complication of the EBB is tracheobronchial ulceration, which may lead to tissue necrosis and fatal hemoptysis. Factors contributing to massive hemoptysis are therapy failure with persistent malignant lung lesions and adjacent major thoracic vessels. Radiation bronchitis and bronchial stenosis are also very common during and after the brachytherapy sessions. An endobronchial narrowing may result from posttherapy edema. The American Brachytherapy Society recommends using a grading classification when evaluating patients with radiation bronchitis and stenosis (see Table 36.4).

Treatment selections are summarized in Table 36.5.

Other complications are pneumothorax, pneumomediastinum, bronchospasm, tracheoesophageal fistulas, and bronchomediastinal fistulas. Pulmonary artery pseudoaneurysm may occur as a late complication as well.

Table 36.4 American Brachytherapy Society modified grading of radiation bronchitis and stenosis

Grade I	Mild mucosal inflammation with swelling, with thin whitish circumferential membrane without endoscopic or clinical evidence of obstruction
Grade II	Greater exudation from the membrane, which might require endoscopic debridement, or steroid therapy, bronchodilator inhalation, oral mucolytics, antitussives
Grade III	Severe inflammatory response with marked membranous exudate
	Multiple debridement or other interventions required to reestablish full lumen of airway
Grade IV	Significant fibrosis requiring balloon or bougie dilation, photoresection, stent placement
Grade V	Necrosis, tracheal, or bronchial malacia or massive hemorrhage related to the treatment without any evidence of invasion of the tumor

Sources: (Data from Nag S, Kelly JF, Horton JL, Komaki R, Nori D. Brachytherapy for carcinoma of the lung. Oncology. 2001 Mar;15(3):37 and Speiser B, Spratling L. Intermediate-dose-rate remote afterloading brachytherapy for intraluminal control of bronchogenic carcinoma. Int J Radiat Oncol Biol Phys. 1990;18:1443–1448, 1–81)

Table 36.5 Treatment of radiation bronchitis

Grade I	Observation
Grade II	Steroid: oral and/or aerosol fluconazole
	Saline diluted bronchodilator
	Narcotic cough suppressants
Grade III	Multiple bronchoscopic debridements
Grade IV	Balloon or bougie dilatation
	Laser photoresection
	Debridement
	Stents

Source: Speiser BL, Spratling. Radiation bronchitis and stenosis secondary to high dose rate endobronchial irradiation. Int J Radiat Oncol Biol Phys. 1993;25(4):589–97

Treatment and Complication Grading

The American Brachytherapy Society highly encourages a quantitative grading of the symptoms experienced by the patient (see Table 36.1), the bronchoscopic findings (see Table 36.2), the tumor response to the brachytherapy treatment, and the complications (see Tables 36.4 and 36.5). These grading systems help in establishing a unified format to follow up the patient's treatment response and progression, as well as aiding in intrainstitutional comparison and clinical trials.

Documentation

Ideally, treatment should be documented in detail. A standardized recording sheet for brachytherapy treatment should be adopted. Having this standardized treatment record helps in coordinating the therapy of patient populations who undergo EBRT and/or chemotherapy, in addition to the brachytherapy. Other requisite documentation should include the following:

1. *Radiotherapy prescription:* Includes instructions on how to deliver the radiation dose to the targeted tissue. It also serves as an alert to the staff involved in treating the patient if the patient is receiving other treatment modalities (EBRT or chemotherapy) whereby dosage adjustment is needed.
2. *Written directives*: Include instructions from the physician to the physics staff and therapists on how to apply the brachytherapy methodology. This should include the isotope, dose rate, targeted site, type of applicator, type of the implant, and duration of the placement.
3. *Isotope recording forms:* Include documentation regarding the numbers and types of the isotope sources, the location of each one of them, and the period of delivery.
4. *Quality assurance*: Each medical center providing brachytherapy should develop an internal quality assurance process to ensure compliance, provide process documentation, and ensure safe practices.

Conclusions

An endobronchial brachytherapy (EBB) targeting central airway lesion is a useful localized radiation therapy modality in patients with symptomatic malignant endobronchial lesions who develop dyspnea, cough, hemoptysis, or collapsed lung. It helps in relieving the symptoms and increasing pulmonary function and exercise tolerance. It may be used alone or in combination with other endobronchial intervention techniques. High-rate dose (HRD) is becoming the most common type of brachytherapy for treatment. It enables brachytherapy to be performed as an outpatient procedure and shortens the total treatment time. EBB requires a multidisciplinary approach between the pulmonologist and the radiation oncologist to organize an adequate treatment plan and follow-up protocol to yield favorable therapeutic outcomes.

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Photodynamic Therapy

37

Chakravarthy Reddy

Introduction

Photodynamic therapy (PDT) has evolved to be an important tool for the management of endobronchial tumors in the practice of interventional pulmonology. It is a nonsurgical, local therapy that involves intravenous injection of a photosensitizing drug followed by activation of the drug at the tumor site with light of a specific wavelength. The requirement for direct light application to the tumor to activate the drug limits the use of PDT to lung cancer that is localized to the airways which are accessible to bronchosocpy. The utility of PDT has expanded and it is currently approved in the United States by the Food and Drug Administration (FDA) for the management of endobronchial non-small cell lung cancer (NSCLC), esophageal cancer, Barrett's esophagus, macular degeneration, and actinic keratosis. Although reports of the utility of PDT in a wide variety of cancers continue to grow, this chapter will primarily focus on the use of PDT in the management of endobronchial tumors.

History

Photodynamic therapy in its current form involves photosensitizing drugs and the use of light to activate the drug in the tumor. History of PDT can be best discussed in terms of the evolution of the individual aspects involved.

History of Phototherapy

Phototherapy is used to describe the use of light alone for treatment of a disease. Therapeutic effects of sunlight were known for centuries. Herodotus, a renowned Greek physician of the second century BC, described the practice of exposing the body to sunlight for restoration of health. In the nineteenth century, Cauvin described sunlight as a form of treatment for rickets. Niels Finsen, a Faroese physician, developed phototherapy into a scientific field and was awarded the Nobel Prize for his pioneering work on the use of artificial light in the treatment for vitiligo and small pox. The best-known practice of phototherapy today is in the treatment of neonatal jaundice.

History of Photochemotherapy

Photochemotherapy or photodynamic therapy describes the process of combining light and an exogenous photosensitizing agent to achieve the therapeutic results. The practice of repigmentation of vitiligenous skin using psoralens extracted from the seeds of *Psoralea corylifolia* was described in the ancient Hindu text *Atharva-veda* in 1,400 BC, and this may be the earliest documented use of PDT. In the twelfth century, the Egyptians extracted psoralens from the plant *Ammi majus* to treat leukoderma. Not much is known about the development of PDT until the beginning of the twentieth century. In 1900, Oscar Raab, a medical student working under Professor Herman von Tappeiner, was conducting an experiment on the effects of acridine (a coal tar derivative) on paramecia. He noticed significantly different toxic effects of the same dose of acridine on paramecia on two separate occasions. He observed that the only noticeable difference was the occurrence of a thunderstorm during one of the experiments that changed the light conditions. The change in ambient light appeared to correlate with an increase in the toxicity of acridine on the protozoan. He went on to conduct further experiments and to subsequently describe the optical property of fluorescence and its in vitro toxic effects. Also in the same year, Prime, a French neurologist, described the photosensitizing effects in sun-exposed skin following oral administration of eosin for the treatment of epilepsy.

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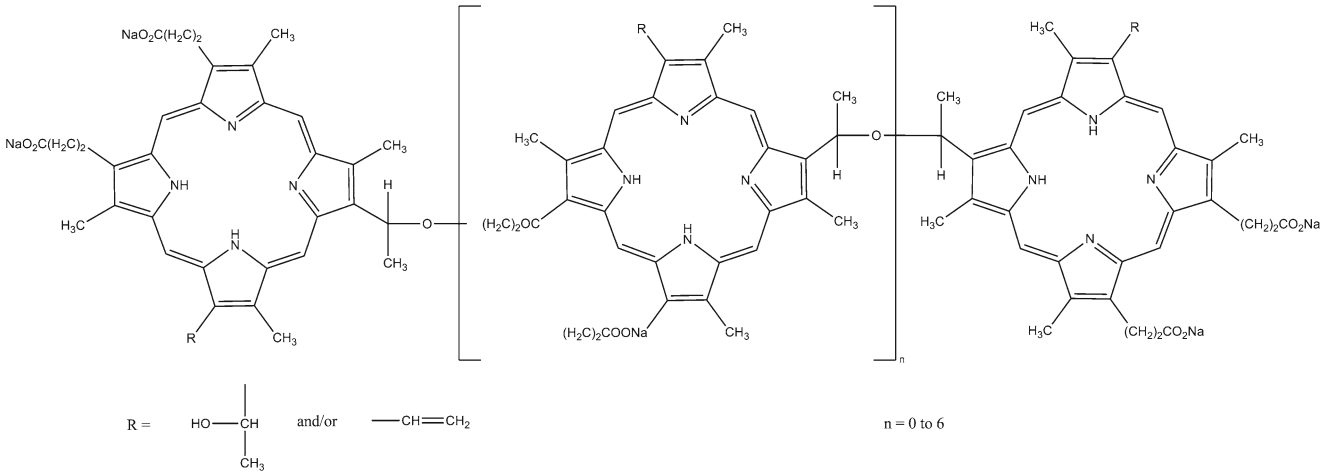

Fig. 37.1 Chemical structure of porfimer sodium

Following Raab's initial findings, Professor Herman von Tappeiner continued working on photosensitizers and along with Jesionek, a dermatologist, described the application of eosin followed by exposure to white light to treat skin affected by tumor, lupus, or condylomata. He also described the phenomenon of oxygen-dependant photosensitization and coined the term "photodynamic therapy."

History of Hematoporphyrins

The drugs used as photosensitizers are crucial to PDT as are the hematoporphyrins (HP), which are the precursors to the currently used photosensitizers. Hematoporphyrins were first extracted from blood in 1841. Fluorescent and the cytotoxic effects of HP were well known by 1908. The first human study with HP was conducted in 1913 when a German scientist, Friedrich Meyer-Betz, injected himself with 200 mg of HP and reported a painful photosensitivity reaction in light-exposed areas that lasted for over 2 months.

The affinity of endogenous porphyrins for tumors was first described by Policard in 1924 when he noticed spontaneous fluorescence on tumor tissue under Woods lamp. Concentration of exogenously administered HP in tumors of experimental animals was the next step in the development of PDT. Selective retention of HP in tumors led to interest in utilizing it as a diagnostic tool; however, large doses were required and the associated phototoxicity made it unsuitable for this purpose.

Hematoporphyrin derivative (HpD), a purified form of HP with a higher affinity for tumors, was extracted by Schwartz et al. in 1955. Focus shifted thereafter from HP to HpD in the development of PDT. Localization of exogenously administered HpD in humans with tumors in the bronchus, esophagus, and cervix was subsequently reported. The first case report of the use of PDT with HpD was published in 1967 with a patient with recurrent breast carcinoma treated with multiple administrations of HpD, followed by exposure of the tumor to filtered light from a xenon arc lamp. The first human study with PDT was conducted in 1976 on patients with bladder cancer. Dougherty conducted the first systematic human trial with PDT in 1978 with the treatment of 25 patients with 113 cutaneous or subcutaneous malignant tumors (squamous cell carcinoma, basal cell carcinoma, malignant melanoma, and metastatic tumors from the breast, colon, or the endometrium). All patients were treated with HpD and exposure to red light from a xenon arc lamp 24–168 h later. Ninety-eight lesions completely regressed, 13 had a partial response, and 2 showed no response, proving the efficacy of PDT.

Photodynamic therapy was limited to the lesions on skin surface prior to the clinical availability of endoscopes. In the 1980s, PDT began to be used through endoscopes for the first time in the management of endobronchial or esophageal tumors. The role of PDT in cancer therapy continues to grow, and over the years, PDT has been shown to be effective in a wide array of tumors including gynecological tumors, intraocular and orbital tumors, brain tumors, cancers of the head and neck, and rectal cancer.

Photosensitizing Drugs

Photosensitizers used for PDT are derivatives of hematoporphyrin, which is extracted from heme. Hematoporphyrin derivative (HpD) was found to have a more stable composition and a higher affinity for tumors when compared to HP. In 1984, Dougherty et al. further purified HpD and extracted the active component bis-1-[3(1-hydroxy-ethyl)deuteroporphyrin-8-yl]ethyl ether (1) or abbreviated as dihematoporpyrin ether (DHE). Dihematoporphyrin ether, better known as porfimer sodium (Fig. 37.1) ("Photofrin," Axcan Pharma) is

the commercially available photosensitizer used currently for PDT. Porfimer sodium has significant side effects and research is under way to develop second-generation photosensitizers that have more selective tissue localization and lower risk of skin photosensitivity and are capable of absorbing light of longer wavelength so that tissue penetration is enhanced. Second-generation photosensitizers that are being evaluated and may prove to be useful in lung tumors are as follows:

(a) Meso-tetrahydroxyphenylchlorin (mTHPC) is a highly active photosensitizer that requires a very low drug dose and is activated by light of wavelength of 648 nm.
(b) 5-Aminolevulinic acid, when administered orally, is metabolized by tissues to a photosensitizer, protoporphyrin IX (PpIX). It is cleared rapidly from the body and the skin photosensitivity effects last for 24 h.
(c) Lutetium texaphyrin is a synthetic water-soluble compound that is activated by red light in the wavelength range of 720–260 nm, giving greater depth of penetration. It is being studied for cervical, prostate, and recurrent breast cancers.
(d) Tin ethyl etiopurpurin is a chlorin photosensitizer that has been studied in recurrent cutaneous metastatic breast carcinoma and showed good response without any photosensitive reactions.
(e) Photochlor or 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide, an HPPH, is a chlorin-type photosensitizer that absorbs light at 665 nm, giving a better penetration, that is being studied in phase I/II trials for local or advanced lung cancer.
(f) Mono-L-aspartyl chlorine e6 (NPe6) or talaporfin sodium has been studied in early superficial squamous cell carcinoma of the lung and in central airway lesions greater than 1 cm in diameter. Light activation can be performed at 4 h from administration of the drug and the skin photosensitivity lasts less than 2 weeks. Being activated with light at 664 nm wavelength, it penetrates deeper and can be effective against more invasive tumors.

Light Source

Conventional lamps with filters were initially employed for photoactivation in PDT. While they were relatively inexpensive and easy to use, they produced a significant amount of heat and wide spectra of wavelengths, making calculations of delivered light doses difficult. Lasers, on the other hand, produce a monochromatic light of a specific wavelength, simplifying dosimetry calculations and allowing light transmittal through a flexible optical fiber. Various types of lasers have been used in PDT. Argon dye lasers can be used to activate different photosensitizers because of the capability

Fig. 37.2 Potassium-titanyl-phosphate (KTP) dye laser unit

to alter the wavelength of the light produced by adjusting the filters. Potassium-titanyl-phosphate (KTP) dye laser is readily available in surgical settings and can be fitted with a PDT dye unit (Fig. 37.2). The unit itself can be expensive and bulky. Diode lasers employ semiconductor diode technology. Their main advantages are the compact nature of the laser units and use of standard electrical outlets, making them relatively more portable. The disadvantages are the limited power output and the limitation of a particular laser unit to light of one specific wavelength. A new diode-based system (Diomed Ltd., Andover, MA) is commercially available, compact, and less expensive and is commonly used in clinical settings (Fig. 37.3).

Mechanism of Action

Following intravenous administration, the photosensitizer agent concentrates in tumor tissue, skin, liver, and spleen. The precise reason for this selective retention is unclear and is thought to be secondary to a lower pH or a high concentration of low-density protein receptors on the tumor cells. The exact mechanism of action of PDT is not fully understood and the reason for tumor death is thought to be multifactorial. Upon exposure, porfimer sodium absorbs the light and

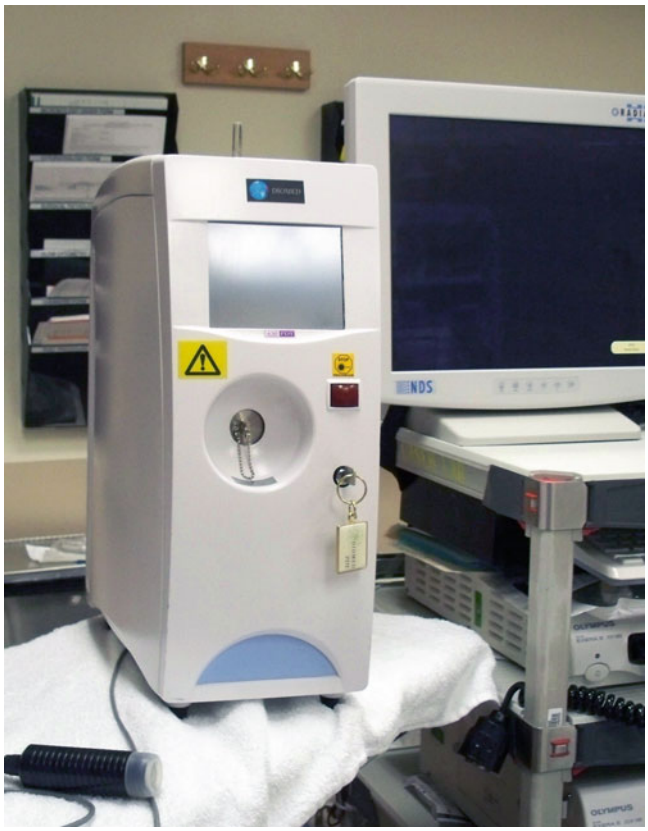

Fig. 37.3 Diode-based laser unit (Diomed Ltd., Andover, MA)

forms a porphyrin excited state and generates singlet oxygen. The resulting superoxide and hydroxyl radical formation causes apoptosis and cell death. In addition, PDT induces small vessel thrombosis mediated by thromboxane A_2 and leads to ischemic necrosis within the tumor. Photodynamic therapy also induces a tumor-specific cytotoxic immunity that can provide a long-term suppression of tumor growth. With the second-generation photosensitizers that are more specific in their effects on tumor, a better understanding of the precise mechanism of action of PDT is anticipated.

Clinical Technique

Drug Administration

Photofrin (Axcan Pharma, Birmingham, AL) is the commercially available porfimer sodium that is used in PDT. The drug is available in 75-mg vials and should be reconstituted according to the package insert prior to administration. Once reconstituted, it should be protected from bright light and administered immediately.

The recommended dosage is 2 mg/kg body weight, and it is a single dose given as a slow intravenous injection administered over 3–5 min. Care should be taken to avoid extravasation at the injection site. If extravasation does occur, the area must be protected from direct sunlight. Photosensitivity precautions discussed below must be enforced immediately after administration of the drug.

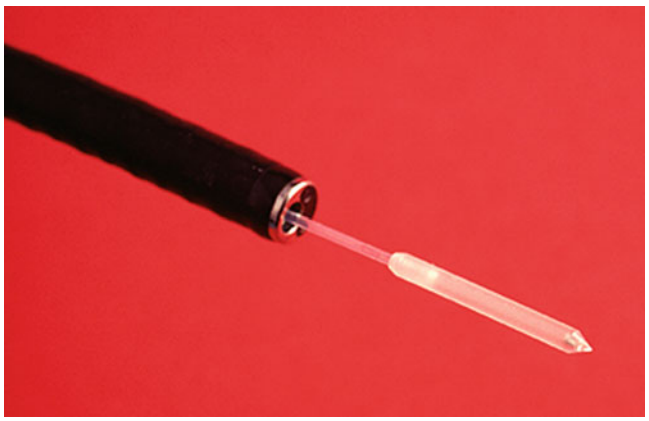

Fig. 37.4 Flexible cylindrical diffuser laser fiber (Courtesy: Armin Ernst)

Photoactivation

Activation of the photosensitizer is performed 40–50 h after administration of the drug. Following the peak plasma concentration after intravenous administration, the drug is distributed into the extravascular compartment including liver, spleen, kidneys, as well as tumors, over the next 24 h. The drug is excreted in bile, and 28 % of the drug is eliminated by 72 h with decreasing concentrations in liver, spleen, and kidneys. Due to selective retention, the concentration of the drug in tumors remains elevated for longer periods, and for this reason, photoactivation is recommended at 40–50 h. If necessary, photoactivation may be performed as early as 24 h following administration of the drug.

Flexible bronchoscopy is performed under conscious sedation or general anesthesia. If possible, tumor debulking should be performed while taking care to avoid excessive bleeding. A cylindrical diffuser laser fiber is then advanced into the airway through the working channel of the bronchoscope to activate the drug (Fig. 37.4). The choice of the length of the diffuser depends on the length of the tumor to be treated. If the tumor is longer than the length of the fiber or if multiple endobronchial lesions are present, PDT can be performed on different segments of the tumor sequentially using the same fiber, during the same procedure. In clinical trials, a light dose of 175–300 J/cm was tested, and the efficacy and safety were similar between the lower and the higher doses. A light dose of 200 J/cm (400 mW/cm) of diffuser length is recommended by the FDA for endobronchial

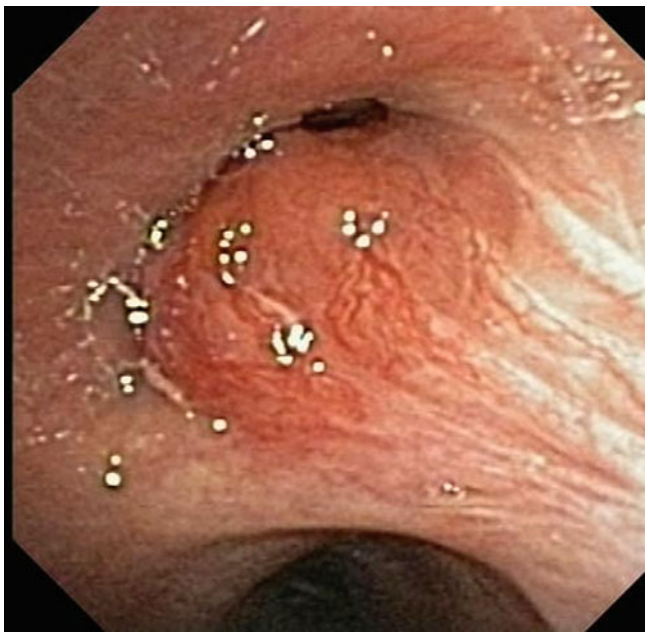

Fig. 37.5 Endobronchial malignant lesion at the secondary carina in the right lung

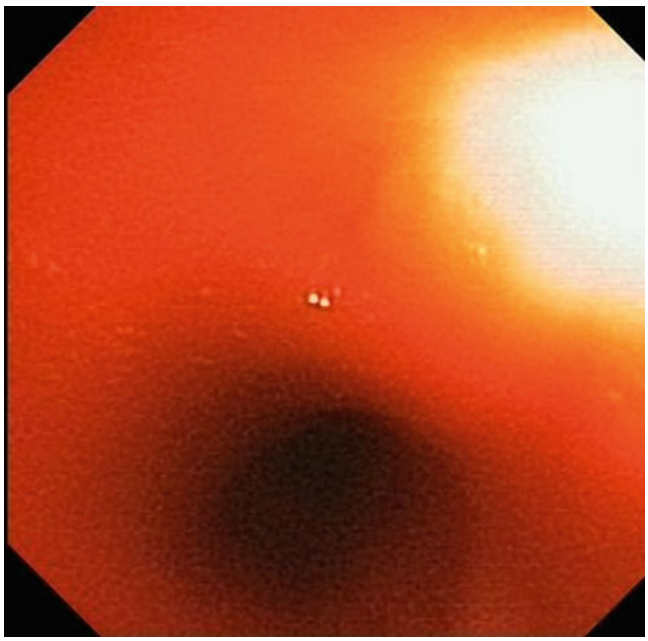

Fig. 37.6 PDT activation at the site to the endobronchial tumor seen in Fig. 37.5

tumors. The diode laser is calibrated such that the total power output at the fiber tip occurs with an exposure time of 500 s. For noncircumferential endobronchial lesions, the tumor can be impaled with the fiber tip to provide intralesional activation without exposing the normal bronchial mucosa to light (Figs. 37.5 and 37.6).

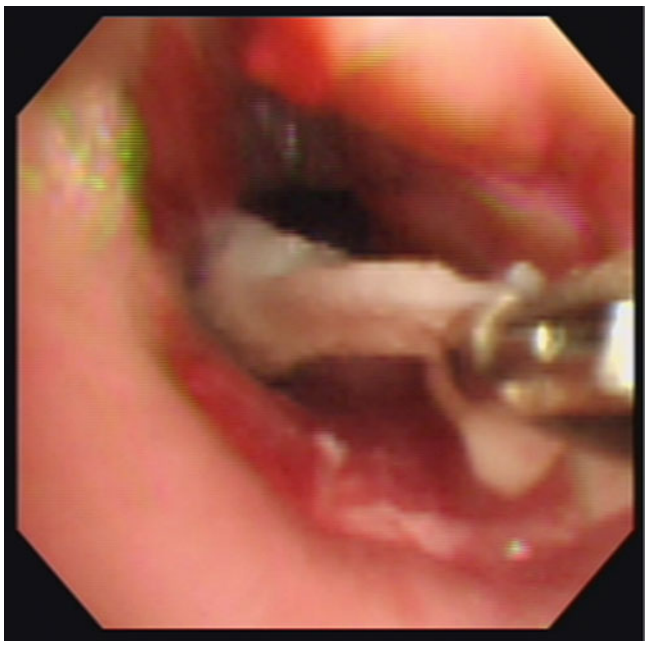

Fig. 37.7 Debridement of necrotic tumor following activation of PDT (Courtesy: Armin Ernst)

Debridement

The tumor undergoes necrosis after activation of PDT and necrotic debris accumulates at the site over the next 48 h. A second bronchoscopy is recommended 2–3 days after each light administration for the purpose of debridement and to prevent airway obstruction from the necrotic tumor slough (Fig. 37.7). If any viable and potentially obstructive residual tumor is present, as evident by bleeding during debridement, a second light application may be performed without the need for another injection of the drug. Residual drug is seen in the tumor for up to 120 h after the initial injection.

If necessary, PDT can be repeated and the current FDA recommendations allow up to three courses of PDT with a minimum of 30-day interval between the treatments. If PDT is being performed after radiation therapy, at least 4 weeks should be allowed between therapies to ensure that the acute inflammation induced by the radiation therapy has subsided prior to PDT.

Indications for PDT in the Lung

Microinvasive Endobronchial Non-Small Cell Lung Cancer (NSCLC)

Patients with early stage NSCLC with the lesions confined to the airway wall typically are treated with surgical resection and have good long-term survival. However, patients may

Table 37.1 PDT in early NSCLC

Reference no.	Author and year	Patients/lesions	Drug	Results
2	Edell and Cortese (1987)	38/40	Hematoporphyrin derivative	CR 30 %; PR 70 %
3	Edell and Cortese (1992)	13/14	Hematoporphyrin derivative	CR 77 %; PR 23 %
4	Ono et al. (1992)	36/39	Hematoporphyrin derivative	CR 30 %
5	Furuse et al. (1993)	51/61	Porfimer sodium	CR 84 %; median survival 20.2 months
6	Imamura et al. (1994)	29/39	Porfimer sodium	CR 64 %; actual 5-year survival 56 %
7	Lam (1994)	22/30	Porfimer sodium	
8	Sutedja et al. (1994)	30/39	Porfimer sodium	CR + PR 97 %
9	Cortese et al. (1997)	21/23	Porfimer sodium	CR 71 %
10	Lam et al. (1998)	102/102	Porfimer sodium	CR 79 %; median survival 2.5 years; median disease-specific survival 5.7 years
11	Kato (1998)	95/116	Porfimer sodium	CR 81 %; 5-year survival 68.4 %
12	Patelli et al. (1999)	23/23	Hematoporphyrin derivative	CR 62 %; PR 38 %
13	Furukawa et al. (2005)	93/114	Porfimer sodium	<1-cm lesion – CR 92.8 %, 5-year survival 57.9 %; >1-cm lesion – CR 58.1 %, 5-year survival 59.3 %
14	Moghissi et al. (2007)	21/23	Porfimer sodium	CR 100 %
15	Corti et al. (2007)	40/40	Hematoporphyrin derivative	CR 72 %; PR 28 %; 5-year survival 59.5 %
16	Endo et al. (2009)	48, lesions <1 cm	Porfimer sodium	CR 94 %; 5-year survival 81 %
17	Usuda et al. (2010)	75/91	Npe6	<1-cm lesion – CR 94 %; >1-cm lesion – CR 90.4 %

CR complete response
PR partial response

not be suitable for a surgical procedure because of comorbid illnesses, poor pulmonary function, a prior pneumonectomy, or the presence of multifocal endobronchial lesions. Photodynamic therapy is approved for use in such patients, with a curative intent.

The use of PDT in the management of early stage lung cancer was first demonstrated by Hayata et al. in 1982. Since then, numerous trials were conducted showing its efficacy and it acquired FDA approval for use in inoperable early stage NSCLC in 1998. The term "early stage" is used broadly, and in clinical trials, this included stage I lung cancer, microinvasive lung cancer, and carcinoma in situ. Synopsis of the major clinical trials in bronchoscopic PDT for early NSCLC is listed in Table 37.1.

Based on available data, no procedure-related mortality has been reported till date, even in patients with poor functional status that rendered them ineligible for surgical options. There was one death 6 h after the procedure from airway obstruction. Although complete response rates varied between 30 % and 100 %, combined complete and partial response rates were over 99 %. When lesions are <1.0 cm in diameter, superficial and all margins can be visualized; completer response rate of >90 % can be achieved with PDT. Mean 5-year survival rate following PDT was surmised at 61 % which is not far below that for surgical resection of stage IA lung cancer (70–80 %).

Completely or Partially Obstructing Endobronchial NSCLC

Airway obstruction with endobronchial tumor is a common complication with primary lung cancers or metastatic lesions to the lung. Various modalities are available to the bronchoscopists for relieving the obstruction. Photodynamic therapy is one of the options approved for palliation of symptoms in patients with malignant airway obstruction. Numerous studies have proved the efficacy of PDT in the management of obstructing endobronchial tumors and are listed in Table 37.2.

Since the effects of PDT are not obvious until tumor debridement 3–4 days after administration of the drug, it is not suitable in patients with high-grade airway obstruction that may cause respiratory distress. If the patients are stabilized on mechanical ventilation following respiratory failure from central airway obstruction, PDT can be used and has been shown to reestablish airway patency and allow extubation.

Although there are no significant differences in short-term effects, photodynamic therapy has a longer duration of

Table 37.2 PDT for palliation of symptoms in advanced NSCLC with airway obstruction

Reference no.	Author (Year)	Patients	Drug	Results
2	Moghissi et al. (1999)	100	Photofrin/ polyhematoporphyrin	Reduction in airway obstruction, improvement in FEV1 and FVC
3	Diaz-Jiminez et al. (1999)	14 randomized to PDT and 17 to Nd:YAG	Dihematoporphyrin ether	PDT group with longer time until treatment failure and longer survival
4	LoCicero et al. (1990)	10	HpD	100 % improvement in symptoms
5	Wieman et al. (1998)	102 randomized to PDT and 109 to Nd:YAG	Photofrin	PDT superior to Nd:YAG at 1 month

symptomatic relief when compared to other modalities used in advanced lung cancer with airway obstruction.

Photodynamic therapy has also been used in combination with other techniques to relieve airway obstruction from malignant tumors. When combined with external beam radiotherapy (XRT), PDT offers more sustained relief of symptoms when compared to XRT alone. Combination of Nd: YAG laser with PDT has been shown to provide a rapid relief in symptoms. Photodynamic therapy has been combined in a sequential manner with brachytherapy in the management of bulky endobronchial tumors.

Nonpulmonary Metastatic Endobronchial Tumors

Although approved in the USA for only NSCLC-related early or late endobronchial tumors, PDT has been found to be clinically useful in the management of nonpulmonary endobronchial metastatic lesions. In a clinical series of 13 patients with endobronchial metastatic lesions from colon cancer, breast cancer, uterine leiomyosarcoma, urinary bladder cancer, renal cell cancer, and gall bladder cancer, an improvement in symptoms was seen in all patients following treatment with PDT. In a series of 27 patients who presented with hemoptysis or dyspnea related to endobronchial metastatic lesions from nonpulmonary primary tumors, PDT achieved acute relief from symptoms in 85 % of patients. In 11 patients with renal cell carcinoma-related symptomatic endobronchial metastases, PDT was used successfully in all cases, without any procedure-related mortality and without a requirement for repeating airway interventions during the 30-day follow-up period. Therefore, PDT may be a reasonable option in patients with symptomatic endobronchial metastatic lesions.

Adverse Reactions

Adverse reactions were reported in 72 % of patients with obstructing endobronchial tumors treated with PDT. Photosensitivity reaction is the most common adverse effect seen following treatment with PDT. Skin photosensitivity (Fig. 37.8a, b) was seen in up to 22 % of patients with endobronchial cancer following treatment with the currently marketed formulation and dose of Photofrin. Patients are at risk for sunburn immediately following the administration of the injection, and the effects last for up to 6 weeks. Patient education is an integral part of the therapy, and instructions on the use of protective clothing and eyewear are essential.

Transient inflammatory response following PDT is seen in 10 % of patients within the first week. Fever, bronchitis, chest pain, and dyspnea are the common manifestations, and these are rarely severe. Pneumonia may occur in up to 10 % of the patients, and a 10-day course of antibiotics may be administered. Dyspnea is often secondary to airway obstruction from the necrotic debris, and debridement of the treated area provides relief. Life-threatening respiratory insufficiency was seen in 3 % of patients.

Hemoptysis was noted in 16 % of the patients. When compared to Nd:YAG, there was an overall trend toward a higher rate of fatal massive hemoptysis in patients treated with PDT, but no significant difference was seen within the first 30 days. The risk of fatal massive hemoptysis increases in patients treated previously with radiotherapy. In patients with no prior radiotherapy, the overall incidence of massive hemoptysis is less than 1 %. Massive hemoptysis occurs more commonly in patients with large, centrally located tumors, cavitating tumors, large tumors extrinsic to the bronchus, or tumors eroding into a major blood vessel.

When PDT is used in the treatment of superficial endobronchial tumors, bronchial ulceration and subsequent airway stenosis are seen in 11 % of the patients. Airway stenosis requiring stent placement occurred in 3 % of patients.

Contraindications and Cautions

Photodynamic therapy with porfimer sodium is contraindicated in patients with porphyria, preexisting tracheoesophageal or bronchoesophageal fistulae, tumor eroding into a major blood vessel, and severe acute respiratory distress caused by an obstructing lesion with an immediate need to reestablish airway patency.

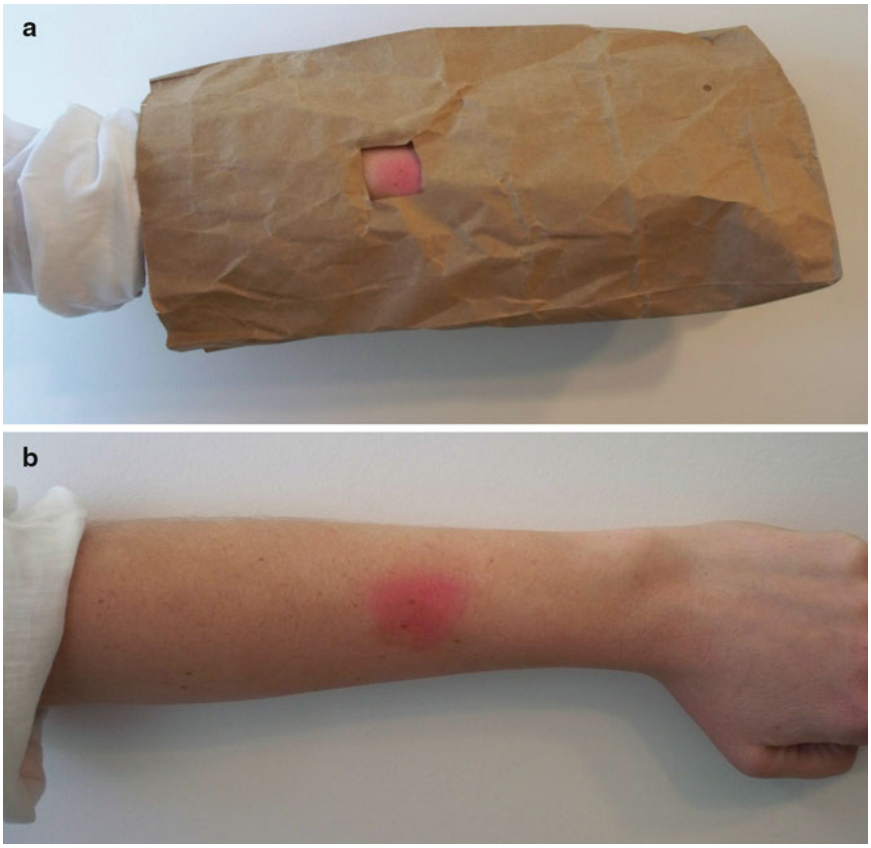

Fig. 37.8 (**a**, **b**) Photosensitivity reaction on sun-exposed area of forearm following PDT

Patients with hepatic or renal impairment may have delayed clearance of the drug and will require photosensitivity precautions for longer periods.

Porfimer sodium is a category C drug for pregnancy, and no data is available regarding its use in nursing mothers.

Financial aspects should be taken into consideration when deciding on utilizing PDT. A vial of porfimer sodium (75 mg) costs 2,878.92 USD (source: Reimbursement Guide, April 2010, Axcan Pharma), in addition to the cost of the endoscopic procedure and the laser fiber.

Conclusion

Photodynamic therapy provides an effective nonsurgical option for the management of early stage NSCLC in the airway or for palliation of symptoms related to airway obstruction from malignant tumors. It complements other modalities available to an interventional bronchoscopist and in experienced hands, has minimal risks to the patients. Emphasis should be placed on adequate patient education to minimize the most common side effect, skin photosensitization. New photosensitizers with more specificity to the tumor tissue and lesser photosensitivity are being developed and will enhance the safety and the efficacy of PDT.

Suggested Reading

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Balloon Dilation Techniques

38

Kevin L. Kovitz

Introduction

Airway stenosis has many causes and has been treated in many ways. The most basic approach is the bronchoscopic dilation of the area of narrowing. While this can be accomplished by various mechanisms, a simple, direct, and minimally traumatic approach is the use of balloons for dilation or balloon bronchoplasty. This chapter will review the patient presentations, technique and equipment, and outcomes expected.

Patient Characteristics

Airway stenosis can be idiopathic or secondary to an underlying disease process (Table 38.1). Patients typically present with dyspnea and may have a focal wheeze on exam. Patients are often misdiagnosed with asthma or other causes of dyspnea and the diagnosis is frequently made after some time. Return of initial symptoms, perhaps slowly progressive, may be a sign of recurrent stenosis in those already treated. A high index of suspicion is required, and this may be assisted by ancillary studies such as imaging (CT with reconstruction better than standard radiographs or tomograms), flow volume loops, and clinical exam. However, the best method for diagnosing the presence, degree, and extent of an airway stenosis is direct visualization via bronchoscopy. Bronchoscopy can assist in establishing the underlying etiology and be therapeutic. Both flexible and rigid approaches apply and will depend on planned intervention, operator and institution experience, and airway stability needs.

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Balloon Characteristics

The main characteristic of balloons (Fig. 38.1) used should be that they are of sufficient length to straddle the stenosis, are of a diameter sufficient to dilate the stenosis, are nonconformal, and generate adequate pressure for dilation. Pressure is generated by a dedicated syringe or inflation device allowing the filling of the balloon with solution (water or saline and may be radiopaque) and measurement of pressure (Fig. 38.2). As for length, ideally the balloon should be able to center over the stenosis with sufficient overlap, approximately ≥1 cm on either side of the stenosis and minimize funneling while inflated. The initial diameter should be small enough to start with a gentle dilation and large enough to dilate beyond the initial diameter of the stenosis. Serial larger diameter balloons may be needed with the resultant largest chosen being several millimeters larger than the desired final diameter of the airway. Serial larger dilations may be accomplished by several different balloons of unique diameter or using balloons that have several inherent diameters depending on inflation pressure. A nonconformal balloon is one that dilates to the desired configuration and diameter without molding to the stenosis. Pressure required for dilation is balloon specific and relates to that needed to achieve the diameter desired.

Technique

As with all patients, attention to airway stability is paramount. Appropriate monitoring and sedation is required. Patients typically require some form of established airway which can be a laryngeal mask airway, endotracheal tube, or rigid bronchoscope depending on location, experience, and planned intervention. Ideally, the practitioner is skilled in all of these options so the approach chosen can be patient specific. With the exception of a very distal stenosis, patient comfort during dilation necessitates a deep degree of sedation or anesthesia. That is, the typical procedure is done with the assistance of anesthesia support and is preferred with all.

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Once the degree and type of stenosis is determined, the approach is chosen. Patients appropriate for balloon bronchoplasty may have this as their only technique used or may have this done in conjunction with other interventions such as airway laser or stenting. In fact, stent deployment or seating may be assisted by the use of a balloon. There are a number of roles for airway balloons (Table 38.2), but as this chapter focuses on balloon dilation, only this will be described.

Table 38.1 Causes of airway stenosis

Intubation
Surgical anastomotic (i.e., sleeve resection, transplant)
Infectious (i.e., tuberculosis)
Inflammatory (i.e., sarcoidosis, Wegener's granulomatosis)
Malignant
Idiopathic
Radiation
Inhalational injury
Malignant stenosis
Trauma

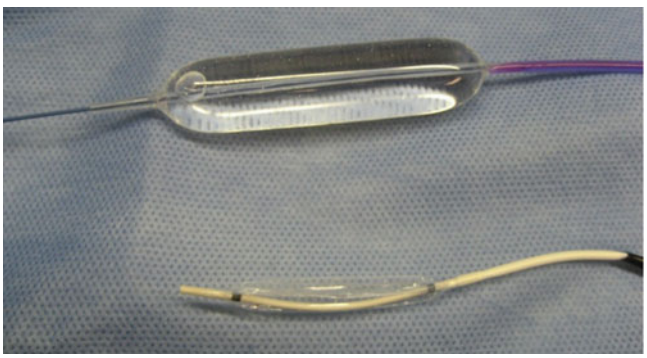

Fig. 38.1 Examples of nonconformal balloons. *Above*: dilated with saline and over a wire. *Below*: a different deflated balloon with radiopaque markers at balloon ends (Boston Scientific, Watertown, MA)

Many balloons are available on the market for use. Balloons specifically marketed for airway use as well as others designed for vascular or gastroenterologic uses have been employed. Balloons for gastroenterologic or bronchosocpic use are often less expensive than those developed for vascular use. Although the pictures in this chapter show product from one company (Boston Scientific, Watertown, MA), this is not an endorsement of one product set or company. Some fit through the working channels of flexible bronchoscopes (Fig. 38.3), while others require placement via a larger channel either directly or over a wire (Fig. 38.4). The larger channel may be a rigid bronchoscope or other airway. The independent passage of a wire and then balloon with image guidance to an area of stenosis and subsequent dilation without bronchoscopic guidance should be discouraged.

Once an airway is established, the bronchoscope is advanced to the area of stenosis. Depending on the balloon and scope used, the balloon is advanced through the working channel of the bronchoscope or over a wire and fed across the stenosis. Bronchoscopic observation of positioning and dilation is ideal. If placed over a wire, the balloon can be observed using a telescope or sufficiently small bronchoscope. While fluoroscopic imaging can also be used, it is rarely necessary as Mayse has demonstrated. Once positioned straddling the lesion, the balloon is inflated to the desired diameter for 1 min and then deflated. Adequate preoxygenation should be established prior to dilation. The 1-min interval is typically repeated at the chosen diameter for a total of three dilations. If limited resistance is encountered,

Table 38.2 Other balloon uses

Stent deployment
Tamponade of bleeding
Deliberate airway occlusion
Foreign body removal

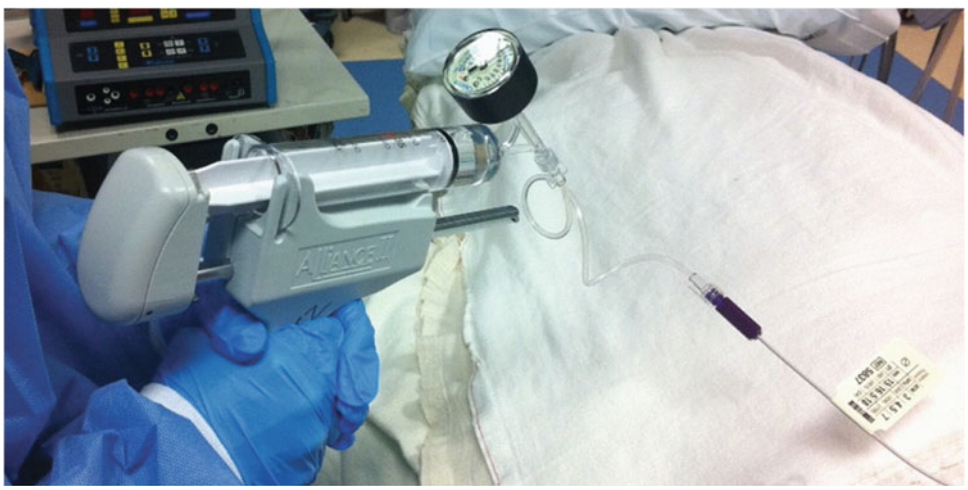

Fig. 38.2 Example of an inflation syringe system with built-in pressure gauge (Boston Scientific, Watertown, MA)

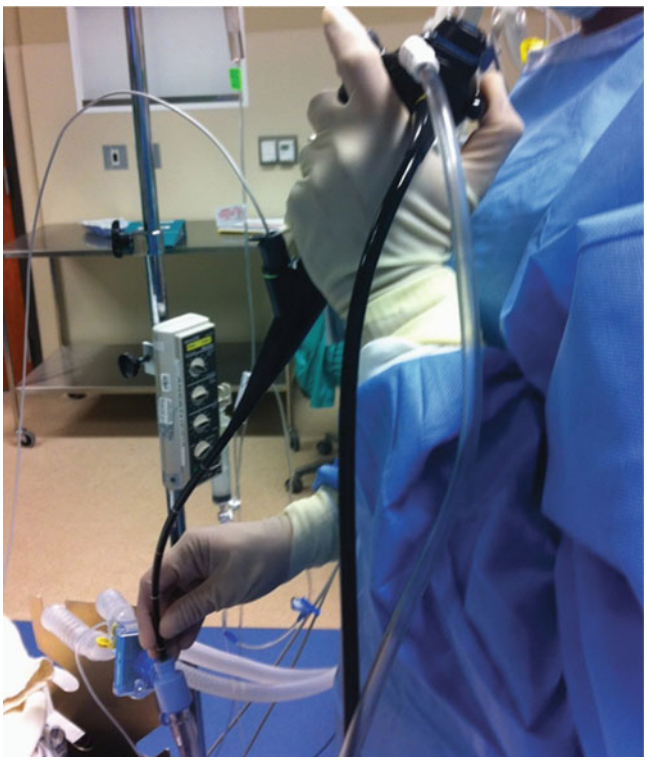

Fig. 38.3 Example of a balloon catheter passed via the working channel of a flexible bronchoscope which is itself inserted into the airway via a laryngeal mask airway

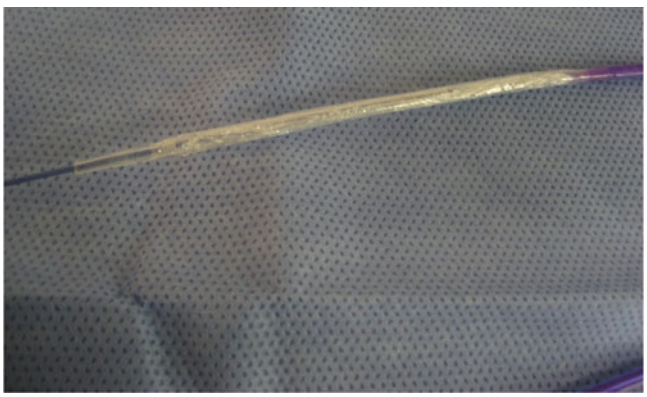

Fig. 38.4 Deflated balloon in its initial state when removed from its package shown with a wire (Boston Scientific, Watertown, MA)

the next larger dilation diameter can proceed before three dilations at a particular level are reached. Different dilation times have been used, but none have been analyzed for superiority. One minute is a reasonable middle ground. The balloon is then deflated and the airway observed for significant finding such as tear or bleeding.

Outcomes

Initial outcomes are excellent (Fig. 38.5) with long-term success requiring repeat procedures at times. Complications are rare (Table 38.3) and typically mild and self-limited. In a small series, Sheski and his colleague had success with an initial procedure in 10 of 14 patients. Adjunct procedures, such as stenting or cryotherapy, and multiple procedures – up to 30 in an extreme case – were required in others. Hebra in a series in children showed a 90% initial and 54% long-term success in tracheal dilation with an average of four sessions. Ferretti, using 1–5 repeat sessions, had a 68% initial success and a 56% long-term success. The lower initial success might be explained by the dilation of some malacia patients in the group. A larger series was reported by Hautmann and colleagues in malignant stenoses and showed better diameter in 79% of stenoses with one procedure, reaching the intended outcome of symptom relief or stenting. Stenting in this case served as an adjunct to other interventions or to lead to better tolerance of other interventions. Most interestingly, Kim and colleagues showed that for benign stenosis patients, laceration of the airway was associated with longer term airway patency. They found that approximately half of dilations led to some degree of airway laceration with the vast majority of

Table 38.3 Potential complications of balloon bronchoplasty

Airway laceration
Bleeding
Pneumothorax
Pneumomediastinum
Mediastinitis
Chest pain

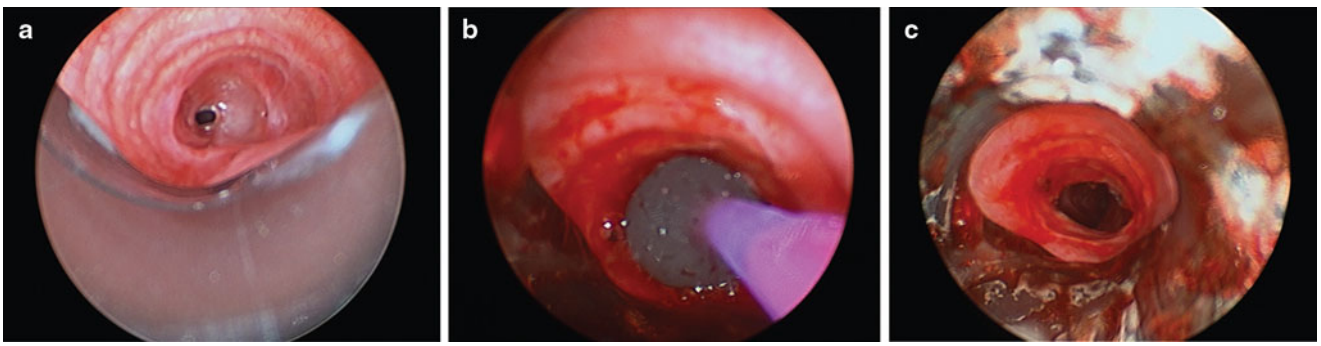

Fig. 38.5 Tracheal stenosis. Before (**a**), during (**b**), and after (**c**) balloon dilation

these superficial. Few were deep, and none were through and through. Some tears had associated mild chest pain, blood-tinged sputum, or even pneumomediastinum, but these all resolved spontaneously at 24 h The tears themselves healed spontaneously in 1 month when superficial and up to 9 months when deep. All were managed conservatively. Patient with tears had an average of 24 months of patency as compared to 4 months for those without a tear. The caveat is that the main etiology of these stenoses was tuberculosis, and the responsiveness or stiffness of the tissue in post tuberculosis stenosis may not apply to all causes.

Lung transplantation represents a common cause of stenosis and a common indication for balloon dilation, often in association with stenting. Stenting may be reserved for the more difficult airway, but the approach likely varies with the institution. Abi-Jaoudeh and colleagues found that they used stents in somewhat more than half of their patients with post-transplant stenosis, but these patients had better symptomatic improvement, longer airway patency, better FEV1, and longer survival. De Gracia also found good initial results in a posttransplant stenosis patient population with subsequent procedures required for an average of four dilation interventions and half ultimately requiring stents.

Conclusions

Balloon bronchoplasty is a safe, simple, quick, effective, and repeatable method to obtain greater airway patency. Symptomatic impact is immediate in most. The equipment is readily available, and supplies are inexpensive. The intervention may be all that is required or can be used as an adjunct to other therapies. If not sufficient, it can at least allow for time to plan for the next levels of intervention.

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Radiation Therapy and Techniques for Fiducial Placement

39

Martin L. Mayse

Background

Radiotherapy is a standard treatment for lung cancer. In years past, its use has been limited by high rates of local recurrence and significant side effects. In the case of early stage non-small cell lung cancer, both recurrence and overall survival rates can be improved by the delivery of higher doses of radiation to the tumor. Furthermore, by focusing and confining the radiation volume to the actual volume of tumor, radiotherapy can achieve similar survival rates and decreased complication rates when compared to less focused and less confined treatment volumes.

The ideally focused and confined delivery of radiation therapy would deliver a lethal dose of radiation to the entire tumor while simultaneously minimizing the radiation delivered to surrounding tissues. To achieve this ideal, it is necessary to have exact knowledge of the size and shape of the tumor, to be able to deliver a tightly focus the radiation beam on just the tumor, and to accurately locate the tumor during entirety of each and every therapy session. While this ideal is not currently possible, much advancement has been made in recent years toward these goals.

For example, high-resolution multidetector computed tomography (CT) scanners and combined positron emission tomography (PET)/CT scanners have increased our ability to accurately determine a tumor's size and shape with insight into the tumor's extension into surrounding structures.

A variety of techniques have also been developed to "conform" the delivered radiation dose to the actual shape and size of the tumor and to "focus" the delivered radiation on the tumor, thereby decreasing the dose delivered to surrounding tissues. One technique uses multiple radiation beams directed at the tumor from multiple different angles, thereby "focusing" the radiation beams on a small volume of tissue. The shape of each beam is also adjusted so that it "conforms" to the contour of the tumor. This then allows the majority of the radiation dose to be delivered to a very focused volume of tissue that has a shape and size very similar to that of the tumor. This is commonly referred to as 3D-conformal radiation therapy (3D-CRT). A similar technique adjusts the intensity of the radiation beam as it is directed at the tumor from multiple directions to "conform" the radiation delivery to the tumor shape and "focus" in on a small volume of tissue. This is referred to as intensity-modulated radiation therapy (IMRT). A third technique uses a single very small beam of radiation that can be moved around the patient and directed at different parts of the target volume form a vast multitude of different angles. This also allows the radiation dose to be contoured to the shape of the tumor and to focus the radiation delivery to a small volume of tissue. All these different techniques are sometimes referred to as stereotactic body radiotherapy (SBRT) or image-guided radiation therapy (IGRT). So long as this conformed and focused volume of radiation is coincident with the location of the tumor and the tumor does not move, then the tumor receives the vast majority of the radiation dose and the surrounding tissue receives very little.

Unfortunately, these sophisticated but static methods that shape and focus the volume of delivered radiation to correspond to the known shape and position of the tumor do not account for microscopic tumor extension beyond the radiographic borders of the tumor, errors that occur in daily patient positioning relative to the linear accelerator (linac), and tumor movement secondary to respiratory motion. To overcome these problems and ensure that the entire tumor is located within the treatment volume, static conventional radiation delivery expands the size of the planned treatment volume to include margins of error corresponding to these unknowns. Such a generic expansion of the treatment zone is shown graphically in Fig. 39.1. While this can help ensure that the entire tumor volume is adequately treated, it

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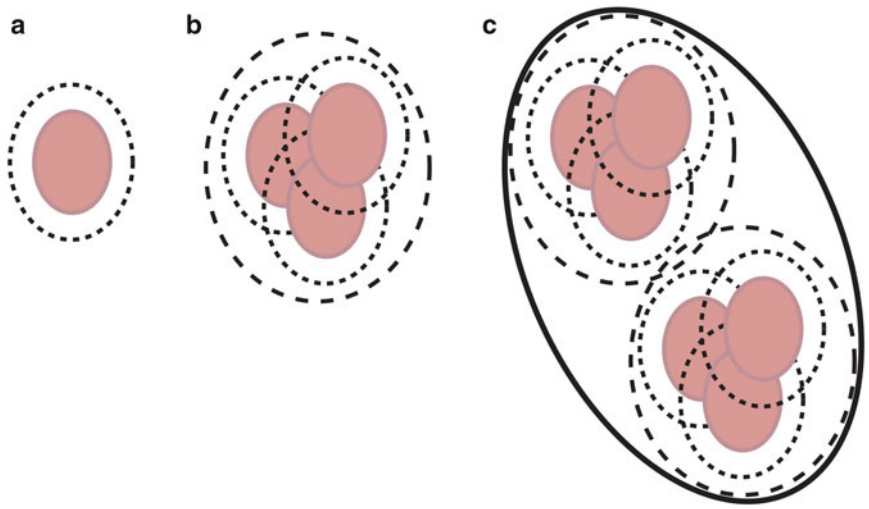

Fig. 39.1 Generic margin expansion to accommodate microscopic tumor extension beyond the radiographic borders of the tumor, errors that occur in daily patient positioning, and tumor movement secondary to respiratory motion. *Panel A* shows a generic tumor. The lightly *dashed line* represents the margin expansion added to increase the volume of planned radiation delivery to accommodate microscopic tumor extension beyond the radiographic borders of the tumor. *Panel B* shows the same generic tumor with its expanded margin as it might appear on three separate days. The variability in position is related to errors in daily patient positioning. The heavy *dashed line* represents the margin expansion performed to accommodate the both microscopic tumor and daily patient positioning errors. *Panel C* shows the same generic tumor with its expanded margins as it might move during respiration. The solid line represents the margin expansion performed to accommodate microscopic tumor, daily patient positioning and respiratory motion. As can be seen, the volume of tissue treated has the potential to be significantly larger than the actual volume of the tumor

diminishes much of benefit possible by shaping and focusing the delivered radiation volume. Additionally, this generic expansion is not one size fits all: Apical tumors typically move less than basilar tumors, central tumors move less than peripheral tumors, larger tumors move less than smaller tumors, and the lung does not follow the same trajectory during every breath in a given patient.

To take full advantage of the tightly focused and conformed radiation delivery volume, it is necessary to know where the tumor is actually located from day to day and breath to breath. Since direct visualization of the tumor is not possible while the X-ray beam is actually on, and even when the beam is off, it is often difficult to visualize the tumor on fluoroscopy, surrogate markers that can be easily seen of continuously tracked can be placed in or near the tumor target. These surrogates are called fiducials; their use, variety, implantation, and the reported experience with them are discussed in the following.

Fiducial Markers and Their Use

A fiducial marker, or fiducial, is a small object placed on or in the body to mark an area for subsequent diagnosis or treatment. In the field of radiation therapy, internally implanted fiducials are used as localizable and trackable surrogates of tumor location. Their value arises from the fact that many soft-tissue tumors are difficult to visualize on fluoroscopy. And even on CT scan images when it is easy for the human eye to identify the location and extent of the tumor, it remains very difficult for automated computer hardware and software to do this same identification. To overcome this, radiopaque metallic fiducials provide very high contrast on both fluoroscopy and CT scan images and are therefore easier to detect by both the human eye and the automated computer hardware and software. The position of these fiducials can be determined at the time of setup prior to the initiation of radiation delivery, and even during the treatment session, their position can be determined by intermittently turning the radiation beam off.

Alternatively, some markers act as wireless electromagnetic transponders (Beacon® Transponders, Calypso Medical Technologies Inc., Seattle, WA, USA) and are radiopaque and can also be localized and tracked in a manner analogous to that used for electromagnetic navigational bronchoscopy. These sorts of markers can be localized using the same methods and with the same limitations experienced with standard fiducial markers but also be localized and tracked by dedicated equipment while the radiation beam is on.

Fiducials potentially allow a more focused delivery of radiation with narrower treatment margins to be used. This can be accomplished by combining a method of conforming

and focusing the radiation beam to the size and shape of the tumor with (1) improved patient setup, (2) respiratory gaiting, and (3) real-time tumor-tracking radiation therapy.

Daily errors in patient setup occur because the patient is not placed in the exact same position relative to the linac every day. By more accurately knowing the location of the tumor target on the day of treatment, the margin expansion to accommodate errors in patient setup (the margin expansion from panel A to panel B in Fig. 39.1) can be decreased.

Respiratory gating is a method of turning the radiation beam on when the tumor target is located at the focal point of the radiation beam and it is turned off as soon as the target moves outside of the beam. The patient is typically aligned so that the beam is on during expiration. Such gating also allows the margin expansion to accommodate respiratory motion (the margin expansion from panel B to panel C in Fig. 39.1) to be decreased.

Real-time tumor tracking is a method of dynamically moving the focal point of the radiation mean so that this focal point always corresponds with the position of the tumor target. Such gating allows the margin expansion to accommodate respiratory motion (the margin expansion from panel B to panel C in Fig. 39.1) to be decreased.

While a variety of radiation therapy systems are capable of real-time tumor tracking, based on the published literature, the system most widely used in conjunction with fiducials is the CyberKnife® (Accuray, Sunnyvale, CA) system. The CyberKnife (Fig. 39.2 panel A and B) consists of a small 6-MV linac mounted on a computer-controlled robotic arm capable of moving with 6° of freedom, two orthogonally placed X-ray, two optical cameras, and an optic-radiographic motion monitoring system for real-time tumor tracking. Radiopaque fiducial markers implanted in or near the tumor and light-emitting diodes placed on the patient's chest are used for target tracking. Prior to radiation treatment and while the X-ray beam is off, a series of X-ray images are taken by the two orthogonal cameras at various times during the respiratory cycle and the system develops a mathematical model relating the locations of the light-emitting diodes on the chest with those of the fiducials near the tumor in the lung. Continuous tracking of the light-emitting diodes combined with this mathematical model allows the robotic arm to be moved in real time such that the radiation beam tracks the moving tumor target. At regular intervals during treatment, additional orthogonal X-ray images are taken to allow the model to be validated and updated with small changes in breathing patterns. The total system accuracy of the device and the respiratory motion tracking has been reported as <1 mm. The current system allows for a dozen different beam directions from over a 100 different robot arm locations, providing more than 1,200 possible beam paths.

Desired Positioning and Implantation Planning

The goal of fiducial marker implantation is to provide enough useful and accurate information to the radiation oncologist to make the added effort and risk worthwhile for the patient. There are several goals to consider when deciding the number and location of fiducial implantation.

When considering the number of fiducials to implant, enough fiducials should be place to provide accurate positional information and ideally rotational information as well. Two fiducials located in and around the tumor such that they bracket the bulk of the tumor can provide translational information about the tumor target. Three fiducials located in and around the tumor such that they bracket the bulk of the tumor and do not overlap on the fluoroscopic tracking system can provide both translational and rotational information. Additionally, enough fiducials should be placed so that it is possible to tell if a fiducial has migrated out of position and ideally enough so that you can tell which of the fiducials have migrated. Migration can be detected by simply measuring the distance between pairs of fiducials at the same phase of respiration and if a significant change in this distance has occurred, then one of the two fiducials has migrated. When only two fiducials have been implanted, it is possible to tell that one of the fiducials has moved, but not which one. When three or more fiducials have been implanted, by measuring the distance between each fiducial and all the other fiducials, it is possible to tell not only that one of the fiducials has migrated but which one. This fiducial can be ignored and positional and tracking information obtained from the remaining fiducials.

When considering where to implant the fiducials, they should be close enough to the tumor target so that they move with the tumor and provide accurate information about the tumors location and motion. They should be far enough away from each other so that each fiducial provides independent information; fiducials implanted very close to one another look like a single fiducial on fluoroscopy. They should not be so far apart that they are outside the field of the view of the tracking system. They should not be positioned such that a straight line can be drawn between any three of the fiducials; such collinear fiducials may appear superimposed on fluoroscopy and thus will not provide useful information. Representative positioning of a group of fiducial markers is shown in Fig. 39.3.

Specific recommendations for fiducial implantation are as follows:

- With currently available fiducials, 4–6 should be implanted to so that three remain in place. Should fiducials with less likelihood of migration become available, less could be implanted.

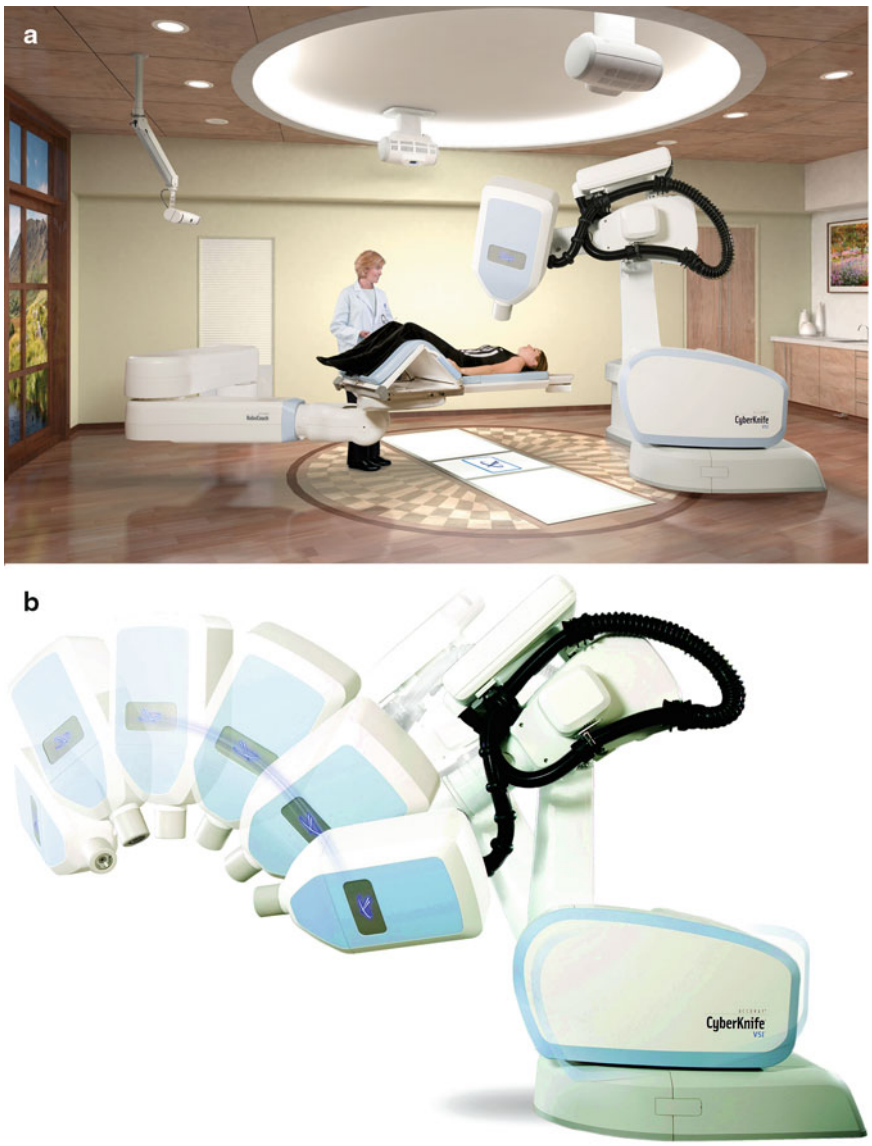

Fig. 39.2 The CyberKnife system consists of a small 6-MV linac mounted on a computer-controlled robotic arm capable of moving with 6° of freedom, two orthogonally placed X-ray, two optical cameras, and an optic-radiographic motion monitoring system for real-time tumor tracking. Radio-opaque fiducial markers implanted in or near the tumor and light-emitting diodes placed on the patient's chest are used for target tracking. Prior to radiation treatment and while the X-ray beam is off, a series of X-ray images are taken by the two orthogonal cameras at various times during the respiratory cycle and the system develops a mathematical model relating the locations of the light-emitting diodes on the chest with those of the fiducials near the tumor in the lung. Continuous tracking of the light-emitting diodes combined with this mathematical model allows the robotic arm to be moved in real time such that the radiation beam tracks the moving tumor target. At regular intervals during treatment, additional orthogonal X-ray images are taken to allow the model to be validated and updated with small changes in breathing patterns. The current system allows for a dozen different beam directions from over a hundred different robot arm locations, providing more than 1,200 possible beam paths. *Panel A* shows an overview of the Cyberknife System with a patient positioned on the couch. *Panel B* shows demonstrates the motion capabilities of the Cyberknife linac (Images used by permission of Accuray Incorporated)

- Fiducials should be placed in and around the tumor, such that the bulk of the tumor is bracketed by the fiducials.
- Those fiducials placed outside the tumor are placed as close to the edge of the tumor as possible and ideally in the same lobe as the tumor. The minimum distance from the edge of the tumor is not known.
- There should be a minimum spatial separation between adjacent fiducials of 1.0–2.0 cm.
- There should be a maximum spatial separation between any two fiducials of approximately 7–10 cm depending on the tracking system.
- Fiducials should not be placed collinearly or positioned such that a straight line can be drawn through any three.

With these recommendations as a guide, planning of the desired implantation sites proceeds in a manner very similar to planning for a biopsy. Unlike planning for a biopsy where

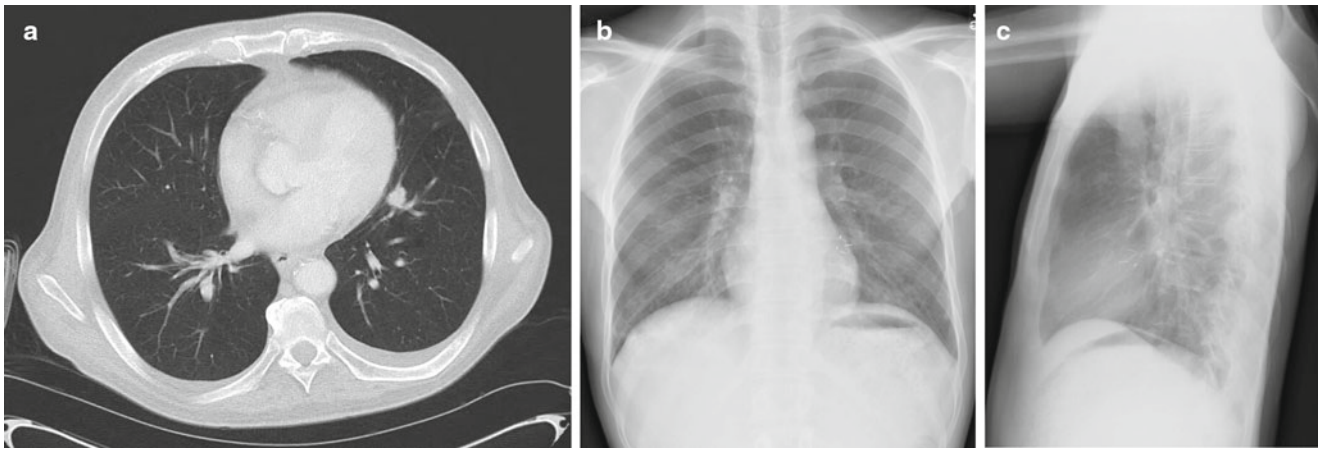

Fig. 39.3 Recommended placement of fiducial markers near a small left sided tumor. *Panel A* shows a cross sectional CT image of the target tumor. *Panel B* and *C* show a posterior-anterior and lateral chest X-ray of the target tumor following implantation of four 0.75 mm diameter coiled wire fiducials in and around the tumor. Note that the fiducials are not collinear on either orthogonal image and while the tumor is not clearly visualized, the fiducials are located such that they bracket and surround the tumor. Also note the close proximity of the tumor to the heart, which makes the tumor very difficult to visualize tumor on these X-ray images

the center of the tumor or lymph node is typically chosen as the target site with the intent to obtain a specimen from the tumor itself, the desired implantation site is often adjacent to the tumor and may actually be a several centimeters away from the center or even the edge of the tumor. This is particularly true for fiducials implanted bronchoscopically into small airways in or near the tumor where the most desirable airway may be some distance from the tumor.

Types of Fiducial Markers

Commercially available fiducial for use in marking lung tumors can be categorized in two basic types: (1) those intended for implantation directly into the tumor or into the lung parenchyma near the tumor and (2) those intended for implantation in small-diameter airways near a tumor. A wide variety of these markers of are commercially available and they are presented in Table 39.1.

Fiducials for implantation into the tumor or lung parenchyma offer the greatest versatility in use. However, care must be taken during insertion to avoid implantation into pulmonary vasculature. In their simplest form, they are small-diameter metallic cylinders with typical diameters of 0.8 mm and lengths of 3.0–5.0 mm. Small-diameter coiled metallic wires are also available with useful diameters of 0.35–0.75 mm and lengths of 10–20 mm. They can be placed in mediastinal lymph nodes, central tumors, or peripheral tumors. They can be implanted percutaneously with a relatively small-bore aspiration needle and guided with computed tomography, fluoroscopy, or ultrasound. They can also be implanted bronchoscopically using an aspiration or biopsy needle passed through the working channel of the bronchoscope, guide sheath, or extended working channel.

Fiducials for implantation into small airways near a tumor are limited to use for tumors with small-diameter airways nearby, although it is possible in more friable tumors to implant these directly into the body of the tumor. In their simplest form, they are metallic cylinders with typical diameters of 0.8–1.6 mm and lengths of 3.0–5.0 mm or 2.0-mm-diameter metallic spheres. Some of the cylinders may have a roughened "knurled" surface, or a diameter that abruptly changes along its length that produces a "stepped" appearance on longitudinal cross section; these shapes are intended to improve stability in when implanted in tissue or an airway. Coiled metallic wires are also available with useful diameters of 0.75–1.2 mm and lengths of 10–20 mm. Implantation is done bronchoscopically with guidance provided by fluoroscopy, electromagnetic navigation, or radial ultrasound.

Transthoracic Method of Fiducial Implantation

Placement of fiducial markers using a transthoracic method is very similar to performance of a transthoracic needle aspiration or biopsy. Following review of the pertinent imaging and localization of the tumor target, the patient is positioned on the procedure table such that the target may be directly and readily accessed through the chest wall. Imaging of the chest with either computed tomography, fluoroscopy, or ultrasound is repeated to again identify the target and to select the proper site for insertion of the needle. The site should be prepped and draped using standard sterile technique.

Table 39.1 Summary of fiducials commonly used in the lung: outlining their shapes, sizes, preferred implantation methods and locations, and sources

Shape	Material	Diameter (mm)	Length (mm)	Surface	Trade name	Source
Implantation into the tumor or surrounding parenchyma with a needle						
Coiled wire	Gold	0.35	20	Ribbed	Visicoil™	Core Oncology, Santa Barbara, CA, USA
Cylindrical	Gold	0.45	10, 20	Stepped cylinder	X-mark™	Onc Solutions, Acton, MA, USA
Coiled wire	Gold	0.5	20	Ribbed	Visicoil™	Visicoil, Core Oncology, Santa Barbara, CA, USA
Implantation into the tumor or surround parenchyma with a needle or into small airways near or in the tumor with a catheter						
Coiled wire	Gold	0.75	20	Ribbed	Visicoil™	Visicoil, Core Oncology, Santa Barbara, CA, USA
Cylindrical	Gold	0.8	3.0, 5.0	Smooth	Gold fiducial marker	Stellar Medical, Fort Meyers, FL, USA
Cylindrical	Gold	0.8	3.0	Knurled	Standard soft tissue	Civco, Orange City, IA, USA
Cylindrical	Gold	0.85	5.0, 10, 20	Stepped cylinder	X-Seed™, X-Mark™	Onc Solutions, Acton, MA, USA
						Stellar Medical, Fort Meyers, FLA, USA
Cylindrical	Gold	0.9	3.0	Knurled	Standard soft tissue	Civco, Orange City, IA, USA
Coiled wire	Gold	0.9	10, 20	Ribbed	FlexiCoil™	Civco, Orange City, IA, USA
Cylindrical	Gold	1.0	3.0, 5.0	Smooth	Gold fiducial marker	Stellar Medical, Fort Meyers, FL, USA
			3.0, 10		Gold seed	Onc Solutions, Acton, MA, USA
Implantation into small airways near or in the tumor with a catheter						
Coiled wire	Gold	1.1	20	Ribbed	Visicoil™	Visicoil, Core Oncology, Santa Barbara, CA, USA
Cylindrical	Gold	1.15	5.0, 10, 20	Stepped cylinder	X-Seed™, X-Mark™	Onc Solutions, Acton, MA, USA
						Stellar Medical, Fort Meyers, FL, USA
Cylindrical	Gold	1.2	3.0, 5.0	Smooth	Gold fiducial marker	Stellar Medical, Fort Meyers, FL, USA
			3.0, 10		Gold seed	Onc Solutions, Acton, MA, USA
Cylindrical	Gold	1.2	3.0	Knurled	Standard soft tissue	Civco, Orange City, IA, USA
Coiled wire	Gold	1.2	10, 20	Ribbed	FlexiCoil™	Civco, Orange City, IA, USA
Cylindrical	Gold	1.6	3.0	Knurled	Standard soft tissue	Civco, Orange City, IA, USA
Cylindrical	Metal and glass	1.8	8.5	Smooth	Beacon® transponder	Calypso Medical Technologies, Inc., Seattle, WA, USA
Sphere	Gold	2.0	–	Smooth	Bone marker	Civco, Orange City, IA, USA

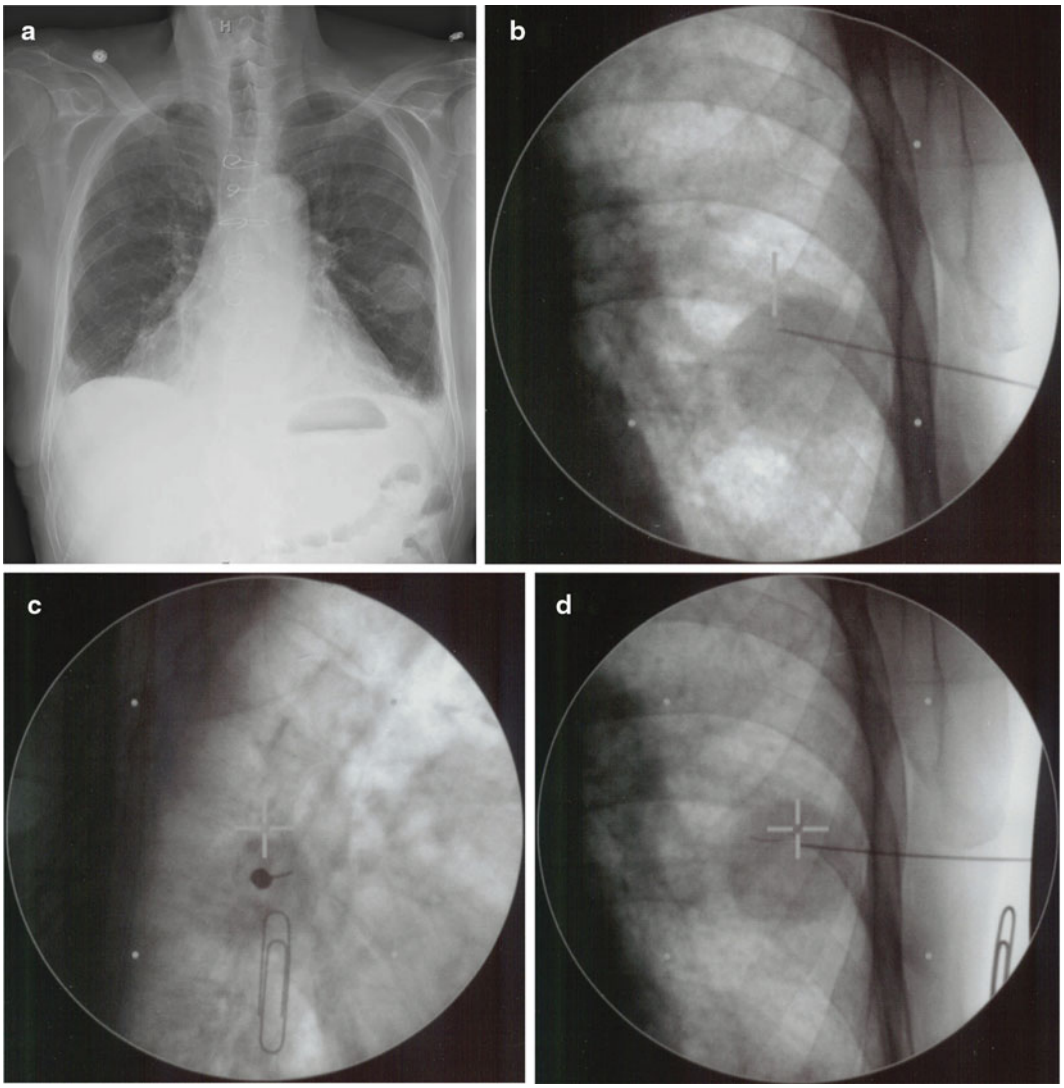

Fig. 39.4 This figure demonstrates percutaneous placement of a fiducial marker in a peripheral pulmonary tumor in the left lung. *Panel A* is a posterior-anterior chest X-ray of the tumor target. *Panel B* shows a posterior-anterior fluoroscopy image of a 18-gauge needle pre-loaded with a 0.75 mm diameter coiled wire fiducial as it is advanced into the tumor target. *Panel C* shows an orthogonal fluoroscopy image of the same 18-gauge needle as it is advanced into the tumor target. Such orthogonal fluoroscopy images allow more accurate positioning of the fiducials in and around the tumor both with this percutaneous approach and when implantation is performed bronchoscopically. *Panel D* shows the fiducial (to the *lower left* of the cross-hairs) in the tumor following deployment

Topical anesthesia is provided to the selected area, with special attention paid to the skin surface, the superior margin of the inferior rib, and the parietal pleura. A fiducial marker preloaded in an introducer needle is selected. Preference to smaller diameter needles is given because they potentially cause lower rates of pneumothorax. A variety of fiducial shapes and sizes are available and come in preloaded needle from most of the manufacturers listed in Table 39.1. The needle is then passed though the anesthetized area and into the desired location in the target tumor or the adjacent lung parenchyma. The needle trocar is then held in place and the needle withdrawn, thereby depositing the fiducial marker in the tumor or lung. Transthoracic implantation of fiducial marker into a peripheral lung nodule using fluoroscopic guidance is shown in Fig. 39.4.

Bronchoscopic Implantation Method

At the 74th Annual Scientific Assembly of the American College of Chest Physicians in Philadelphia, PA, in 2008, I had the opportunity to interview nine interventional pulmonologists with experience placing fiducial markers about the methods they use to place fiducials bronchoscopically; more than nine different methods were described during the course of the interviews. Since there are currently no

commercially available delivery devices for the bronchoscopic implantation of fiducials in the lung, each of these interventional pulmonologists was forced to invent their own technique for implantation using "off-the-shelf" equipment. This is one of the main frustrations when implanting currently available fiducials and should be addressed in future lung markers.

In the following method descriptions, because there is a need to place a given fiducial inside a second device that was not designed for fiducial deployment and has not been tested for compatibility with the fiducials, the descriptions will contain more equipment specifics than are typical in these sorts of discussions. The literature and the authors experience support the compatibility of the specific fiducial/device combinations described, although other combinations are likely possible.

Additionally, all the following procedures assume that the patient has been properly consented, positioned, monitored, sedated, and anesthetized and, if fiducial implantation is part of a diagnostic bronchoscopy, that the other aspects of the bronchoscopic procedure have been completed safely, satisfactorily, and in accordance with best practice.

Mediastinal and Central Implantation Using Endobronchial Ultrasound

Implantation directly into mediastinal lymph nodes, mediastinal tumors, and central tumors using endobronchial ultrasound guidance is one of the easiest techniques to perform and therefore serves as the logical starting point. The basic technique is very similar to endobronchial ultrasound-guided transbronchial needle aspiration (TBNA).

The standard 22-gauge TBNA needle (NA-201SX-4022, Olympus America, Inc., Center Valley, PA, USA) has a removable stylet and can be used for implantation of 0.35-mm-diameter fiducials (Visicoil™, Core Oncology, Santa Barbara, CA, USA). To ensure that the fiducial is not deployed accidently, the stylet should be removed from the needle until the needle is in position within the target. The desired fiducial length for this technique is 5.0 mm to 10 mm. If the available fiducial is longer than this, it should be cut to length. To load the fiducials, the 22-gauge needle is then advanced beyond its protective catheter and the fiducial is inserted into the bore of the needle and sealed in place with sterile bone wax (Fig. 39.5).

The linear EBUS bronchoscope is then advanced into the desired location and the target is located with the ultrasound probe in a manner similar to that used in preparation for TBNA. Assessment with Doppler imaging is appropriate to ensure that there are no larger blood vessels in the planned implantation site. Once the proper position has been identified, the scope is held in place and the catheter with needle retracted is passed through the scope. The needle with the fiducial inside is then advanced under continuous ultrasound guidance into the target tissue. Since the fiducial is going to be pushed out of the needle, room should be left between the tip of the needle and the edge of the target tissue to accommodate the length of the fiducial. With the needle in place and the scope held steady, the stylet is then inserted and passed all the way through the needle, pushing the wax and fiducial out of the needle and implanting them in the tumor target. This is readily seen on ultrasound and fluoroscopy and is shown in Fig. 39.6.

Peripheral Implantation in the Tumor or Surrounding Parenchyma with a Needle

The basics of this technique are very similar to TBNA of a peripheral nodule. The desired implantation site is located using standard fluoroscopy, electromagnetic navigation, radial endobronchial ultrasound probe, or a combination of these tools as described elsewhere in this book. While any of these tools can be used to locate the desired implantation site, we recommend that final positioning of the fiducial and actual deployment of the fiducial be monitored by fluoroscopy. Fluoroscopy provides real-time information about the actual position of the fiducial relative to the target, previously implanted fiducials, tip of the bronchoscope, other bronchoscopic accessories, and the chest wall.

Once the target location has been localized, the fiducial should be loaded into the needle. An appropriately sized combination of needle and fiducial markers is selected. We prefer to use a transbronchial histology needle (WANG® Histology Needle, MW-319; Conmed Endoscopic Technologies, Utica, NY, USA). This needle catheter has a 19-gauge outer needle and a coaxial 21-gauge inner needle that can be retracted independent of the outer needle. While any of the fiducials from Table 39.2 with a diameter ≤0.8 mm can be used, we prefer the larger diameter cylindrical fiducials or coiled wires with a length of 5.0 mm because they tend to fit better in the needle tip and deploy more easily. Deployment can be further improved by using a sterile metal file to flatten the tip of the 21-gauge needle prior to load the fiducial.

To load the fiducial into the needle, the 19-gauge outer needle is extended and a coaxial 21-gauge inner needle is retracted. The fiducial is then carefully inserted into the bore of the needle and sealed into place using bone wax. The bone wax prevents loss of the marker while it is being passed through the bronchoscope. With the fiducial loaded inside the 19-gauge outer needle, both needles are then retracted until their tips are inside the outer protective catheter.

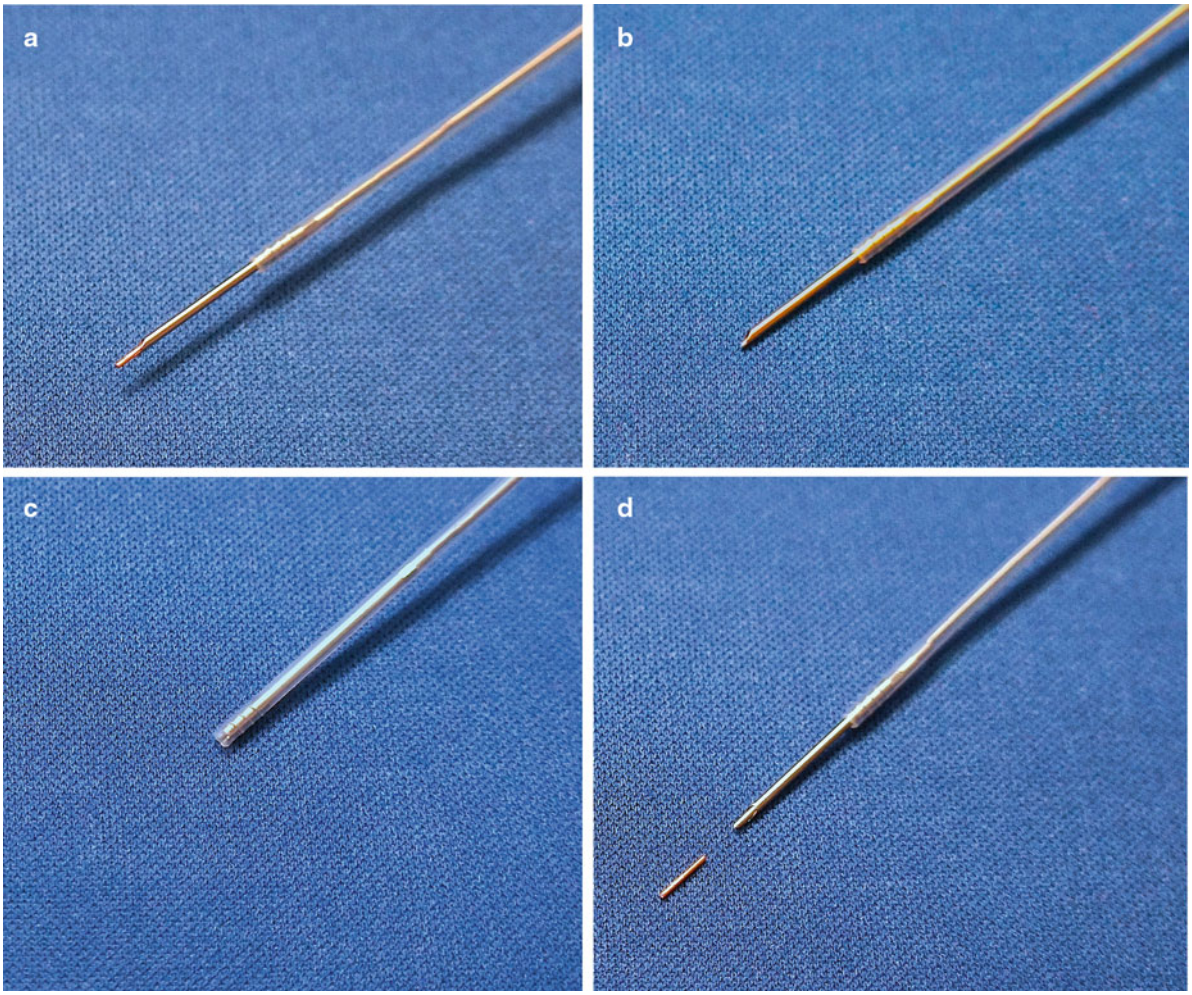

Fig. 39.5 This figure demonstrates loading of a fiducial in a transbronchial histology needle (WANG® Histology Needle, MW-319; Conmed Endoscopic Technologies, Utica, NY, USA) that has a 19-gauge outer needle and a coaxial 21-gauge inner needle that can be retracted independent of the outer needle. *Panel A* shows the 19-gauge outer needle fully extended, the coaxial 21-gauge needle retracted, and a cylindrical fiducial with a 0.5 mm diameter and a length of 5.0 mm partially loaded in the tip of the outer needled. *Panel B* shows the fully extended 19-gauge outer needle after the fiducial has been completely inserted into the bore of the needle and sealed into place using bone wax. The bone wax prevents loss of the marker while it is being passed through the bronchoscope *Panel C* shows the tip of the transbronchial histology needle catheter with both outer and coaxial inner needles retracted and ready for insertion. In use, the needle catheter is then passed through the bronchoscope, or the extended working channel or guide sheath if these are being used, and advanced until the tip of the catheter clears the end of the instrument and is approximately 2 cm proximal to the desired implantation site. The 19-gauge outer needle is then extended and the needle catheter advanced until the tip of the needle is located immediately proximal to the desired implantation site. The coaxial 21-gauge inner needle is then advanced pushing the fiducial out of the bore of the 19-gauge outer needle and depositing it in the desired implantation site. *Panel D* shows the outer 19-gauge and coaxial 21-gauge needle fully extended and the fiducial ejected from the needle

The needle catheter is then passed through the bronchoscope, or the extended working channel or guide sheath if these are being used, and advanced until the tip of the catheter clears the end of the instrument and is approximately 2 cm proximal to the desired implantation site. The 19-gauge outer needle is then extended and the needle catheter advanced until the tip of the needle is located immediately proximal to the desired implantation site. The coaxial 21-gauge inner needle is then advanced pushing the fiducial out of the bore of the 19-gauge outer needle and depositing it in the desired implantation site. Once implanted, the coaxial 21-gauge inner needle should be withdrawn slowly to ensure that the fiducial has cleared the 19-gauge outer needle. Both needles are then retracted and the needle catheter withdrawn.

This procedure is then repeated to implant the desired number of fiducials. After all fiducials are implanted, a post-procedure radiograph was obtained to confirm fiducial placement and exclude iatrogenic pneumothorax.

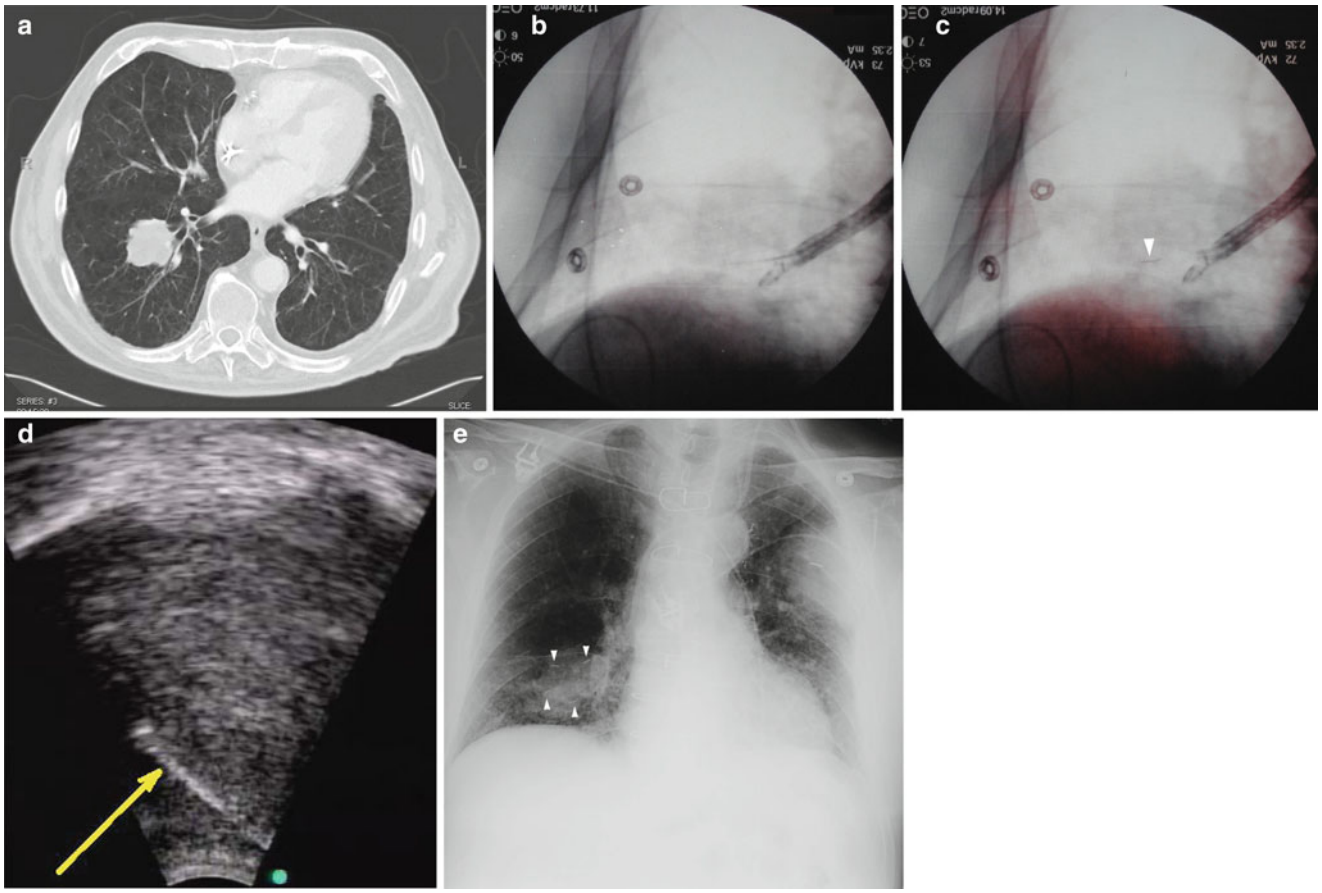

Fig. 39.6 This figure demonstrates implantation of a fiducial in a central tumor using endobronchial ultrasound guidance. *Panel A* shows cross-sectional CT image of the tumor target. *Panel B* shows a posterior-anterior fluoroscopic image of a standard 22-gauge TBNA needle (NA-201SX-4022, Olympus America, Inc., Center Valley, PA, USA) preloaded with a 0.35 mm coiled wire fiducial being passed through an endobronchial ultrasound scope and into the tumor target. *Panel C* shows a posterior-anterior fluoroscopic image of the fiducial (indicated by the white arrow head) being deployed from the needle. *Panel D* shows a near simultaneous ultrasound image of the same fiducial being deployed. *Panel E* shows an anterior-posterior chest X-ray following deployment of four fiducials around the periphery of this tumor target

Peripheral Implantation in an Airway Inside or Near the Tumor with a Catheter

Several options exist for fiducial implantation into an airway inside or near a tumor. You can (1) preload the fiducial in the catheter or (2) after-load the fiducial in the catheter. The goal of such placement is to "wedge" the fiducial in an airway. Hence, the selected fiducial should have a diameter large enough to fit snuggly in the targeted airways.

Preloading the Fiducial in the Catheter

To preload the catheter, first, an appropriately sized combination of catheter and fiducial marker is selected. For the delivery catheter, we prefer to use a microbiology brush (130; Conmed Endoscopic Technologies, Utica, NY, USA) because it comes with a wax plug in its tip. While it is possible to use any of the fiducials from Table 39.1 whose diameter is small enough to fit inside the catheter of the microbiology brush, we prefer cylindrical fiducials with a diameter of 0.8–0.9 mm and length of 5.0 mm or a coiled wire with a diameter of 0.75 mm and a length cut to 5.0–10 mm. These sizes tend to fit well in the catheter and deploy easily from the catheter (Fig. 39.7).

To load the fiducial in the catheter, the fiducial is simply pressed into the wax plug located in the end to the catheter. This wax holds the fiducial in place and prevents loss of the marker as the catheter is passed through the bronchoscope.

The catheter is then passed through the bronchoscope, or the extended working channel or guide sheath if these are being used, and advanced until the tip of the catheter clears the end of the instrument and is located immediately proximal to the desired implantation site. Under fluoroscopic visualization, the brush is then advanced, pushing the fiducial and wax plug out of the bore of the catheter and depositing them in the desired implantation site. Once implanted, the brush should be withdrawn slowly to ensure that the fiducial has cleared the catheter. The catheter is then withdrawn.

Table 39.2 Summary of the all published literature on the clinical experience with bronchoscopically placed fiducial markers placed in small airways around peripheral lung tumors. Patients did not undergo surgery because of tumor stage; existing comorbidities such as old age, poor respiratory, cardiac, and renal function; or refusal to undergo surgery

Author year	Patients	Stage	Type	Total number	Location	Migrated	PTX#	PNA&	Use of fiducial	Follow-up	Time to local progression	Mortality	Comments
Harley 2010	43	–	0.8 mm cylinder	161	Bronchus, parenchyma and tumor	22/161	1/42*	–	Cyberknife®	10–14 days	–	0	Nine tumors located centrally No other complications reported
Imura 2008	7	–	1.5 mm sphere	16	Bronchus	–	–	0/7	Surgery	1–7 days	–	–	Histopathology showed only "slight hemorrhage," "fibrin exudate," "slight fibrotic changes," and "hyperplasia of type II pneumocytes"
Kupelian 2007	8	I	0.7 mm coil	10	Parenchyma and tumor	0/10	0/8	–	Set-up	57–118 days	–	–	One tumor located centrally No comment on long-term complications. Based on provided CT scans, no infiltrate seen on first and last CT scan near the fiducial
Nelson 2008	1	III	–	5	Bronchus and tumor	2/5	–	–	Set-up and gating	–	–	–	No specific report made about complications other than migration
Nelson 2007	5	III	0.9 mm cylinder and 2.0 mm sphere	29	Bronchus and tumor	20/29	0/5	–	Gating and IMRT	44–64 days	–	–	No specific report made about complications outside the immediate period of fiducial placement
Anatham 2007	8	I-IV and mets	0.8 mm cylinder	39	Bronchus and tumor	4/39	0/8	0/8	Cyberknife	7–10 days	–	0/8	Self limited fever in one, and COPD exacerbation in one
Shirato 2006	21	–	1.5 mm sphere	63	Bronchus	–	–	–	–	–	–	–	This study reported tracking results and did not provide any long-term follow-up
Imura 2005	57	–	1.5 mm sphere	154	Bronchus	50/154	1/57	–	Set-up and RTRT	16–181 days	–	–	This study did not specifically report on pulmonary complications
Onimaru 2005	39	–	1.5–2.0 mm sphere	42	Bronchus	–	–	–	–	–	–	–	This study reported tracking results and did not provide any long-term follow-up
Shirato 2003	34	–	2.0 mm sphere	123	Bronchus	3/123	0/34	0/34	RTRT	<1 month	–	–	No "symptomatic complications or infections" were noted
Harada 2002	14	I-III and mets	1.0–2.0 mm sphere	16	Bronchus and tumor	2/16	0/14	0/11	RTRT	5–15 months	–	1/11	Eleven patients were treated and subsequently followed up Only 2 fiducials in 2 patients were 1.0 mm

 # PTX pneumothorax, *& PNA* pneumonia, * Pneumothorax requiring a chest tube, "–"indicates not reported

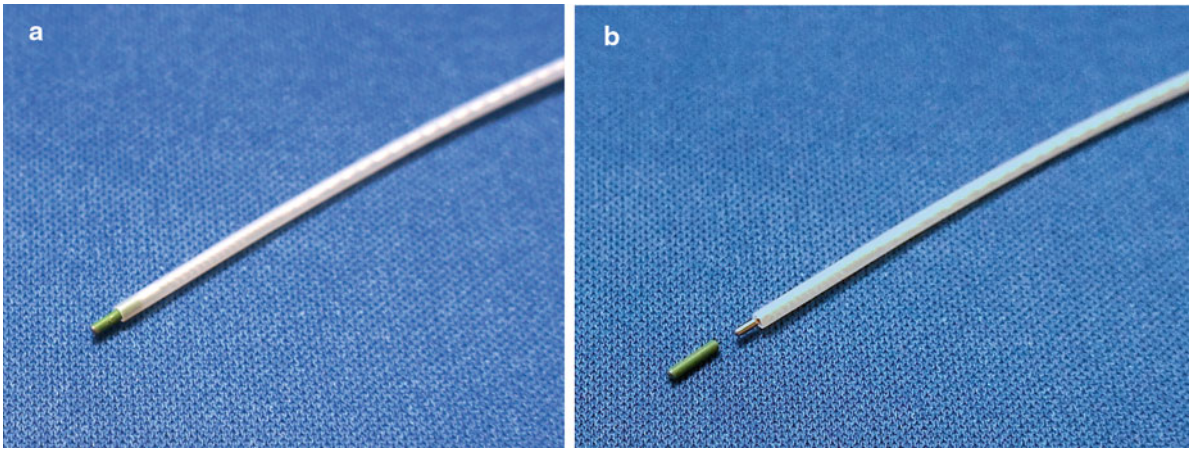

Fig. 39.7 This figure demonstrates pre-loading a fiducial marker into a microbiology brush (130; Conmed Endoscopic Technologies, Utica, NY, USA). This microbiology brush is desirable to use because it comes with a wax plug in its tip. In preparation for preloading, the brush should be fully retracted into the catheter. *Panel A* shows a metallic fiducial (colored green for added contrast) that has partially been pressed into the wax plug located in the end to the catheter. This wax holds the fiducial in place and prevents loss of the marker as the catheter is passed through the bronchoscope. In used, the catheter is passed through the bronchoscope, or the extended working channel, or guide sheath if these are being used, and advanced until the tip of the catheter clears the end of the instrument and is located immediately proximal to the desired implantation site. Under fluoroscopic visualization, the brush is then advanced pushing the fiducial and wax plug out of the bore of the catheter and depositing them in the desired implantation site. *Panel B* shows the ejected fiducial and the tip of the microbiology brush visible just beyond the tip of the catheter. Once implanted, the brush should be withdrawn slowly to ensure that the fiducial has cleared the catheter

This procedure is repeated to implant the desired number of fiducials. After all fiducials are implanted, a postprocedure radiograph was obtained to confirm fiducial placement and exclude iatrogenic pneumothorax. Implantation using this technique is demonstrated in Fig. 39.8.

After-Loading the Fiducial in the Catheter

The original description by Harada in 2002 of bronchoscopically placed fiducial markers in the lung used the after-loading technique.

An appropriately sized combination of delivery catheter, stylet, and fiducial marker is selected. For the delivery catheter, we prefer to simply use a radial ultrasound guide sheath with a 2.55-mm outer diameter (SG-201C, Olympus America, Inc., Center Valley, PA, USA) or an extended working channel (iLogic™ Guide Catheter, superDimension, Inc., Minneapolis, MN, USA). As a stylet, we simply use a cytology brush catheter compatible with these devices, with the brush retracted. Again, it is possible to use any of the fiducials from Table 39.1; however, the larger the diameter, the better it will wedge into an airway. The cylindrical or coiled wire fiducials with a diameter of 1.6 mm and length of approximately 5.0 mm can be passed through with the guide sheath or the extended working channel or a 2.0-mm spherical marker can be passed through the extended working channel. These size combinations tend to allow relatively easy passage of the fiducial through the delivery catheter.

The deliver catheter is passed through the bronchoscope and advanced until its tip is at the desired fiducial implantation site using standard techniques. Once the catheter is properly positioned, the fiducial is carefully loaded in the back of the catheter. The stylet is then inserted in the back of catheter and advanced, thereby pushing the fiducial through the catheter. Under fluoroscopic visualization, advancement of the stylet continues until the fiducial is pushed out the end of the catheter and deposited in the desired implantation site. The catheter can then be withdrawn and the procedure repeated until the desired number of fiducials has been implanted.

Actual Experience with Use and Complication of Lung Fiducials

Fiducial markers have the potential to provide unparalleled assistance to the radiation oncologist; by acting as radiographically visible surrogates of tumor location, they can provide accurate localization and tracking of tumors. This enables the delivery of higher doses of radiation to the tumor target while decreasing the dose to surrounding tissue. This may ultimately increase disease free survival and decrease side effects. Unfortunately, the magnitude of this benefit is not yet clearly defined.

In addition to these real and potential benefits, there are also multiple theoretical risks associated with the placement of fiducials into the lung, the presence of fiducials in the

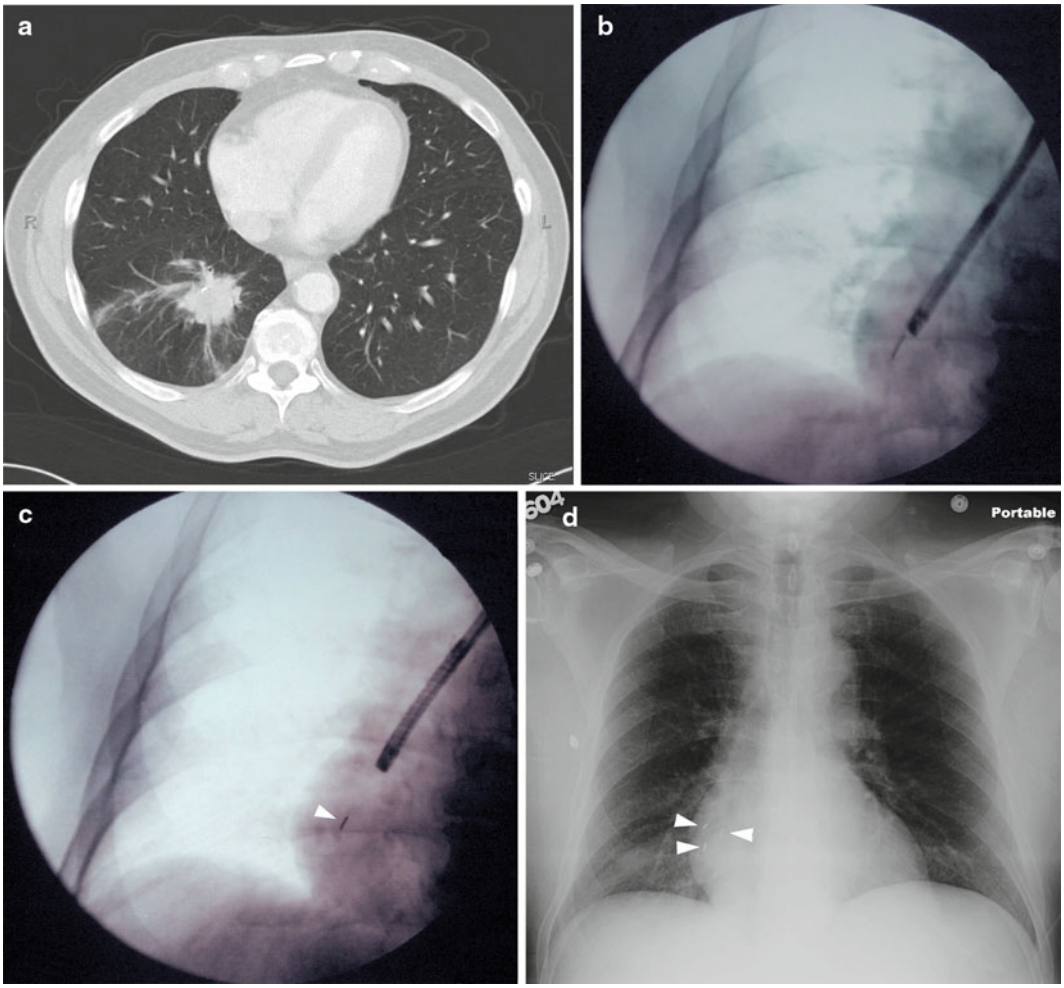

Fig. 39.8 This figure demonstrates bronchoscopic implantation of a fiducial in airways in and around a tumor target. *Panel A* shows cross-sectional CT image of the tumor target. *Panel B* shows a posterior-anterior fluoroscopic image of a microbiology brush catheter (NA-201SX-4022, Olympus America, Inc., Center Valley, PA, USA) preloaded with a 0.75 mm coiled wire fiducial being passed through a bronchoscope and into an airway in the tumor target. *Panel C* shows a posterior-anterior fluoroscopic image of the fiducial (indicated by the *white arrow* head) following deployment. *Panel D* shows an anterior-posterior chest X-ray following deployment of three fiducials in airways in and around this tumor target

lung, and alteration in the delivery of radiation therapy made possible by the fiducials that may have unanticipated detrimental effects on treatment outcomes.

Potential risks associated with placement include all the risks associated with transthoracic needle placement or bronchoscopy. Additionally, the risk of pneumothorax may be increased, and there is the additional risk of fiducial embolization to other organs if it is implanted into a pulmonary blood vessel.

Potential risks associated with the presence of the fiducial are related to a foreign-body reaction, migration, and airway obstruction. Foreign-body reaction may include localized inflammation, mucosal erosion, scar tissue formation, and granulation tissue reaction. Fiducials may migrate out of position over time, subsequently moving to a new location in the lung or becoming free in the airway eventually to be expectorated or swallowed. Implantation of fiducials into airways near the tumor will at least partially obstruct the bronchiole in which it is implanted and may lead to infection.

Lastly, while the goal of fiducial placement is to allow higher radiation doses to be delivered to the tumor and lower doses to the surrounding healthy lung tissue, this may not always be to the patient's benefit. If the fiducials migrate out of position and this is not detected, the radiation may be delivered to the wrong part of the lung. Or if the fiducials allow the margins to be decreased so much that microscopic tumor extends beyond the edge of the treatment zone, then the more focused delivery of radiation made possible by the fiducials may have unanticipated detrimental effects with inadequate treatment of the tumor and potentially high-dose treatment to relatively healthy lung tissue.

To better understand the actual experience on the use of fiducial markers implanted in the lung and complications resulting from their implantation and use, we performed a systematic review of the literature to illuminate this. Because no appropriate MeSH headings exist for "fiducial," on March 18, 2010, we conducted a text search using PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) with the search parameters ("fiducials"[All Fields] OR "fiducial"[All Fields] OR "gold marker"[All Fields]) AND "lung"[All Fields] limited to "English" language and "Human". Ninety-three articles were found. Articles were rejected if they did not report on internally implanted fiducials, did not report clinical outcomes or complications related to the use of implanted fiducials, or were a reanalysis of previously reported data. After review of the abstract or full text of these 93 articles, the 27 original articles that reported results for fiducials placed internally in the lung were selected for inclusion. These articles were then segregated into 11 articles reporting bronchoscopically implanted fiducials and 17 articles reporting percutaneously implanted fiducials.

Percutaneously Implanted Fiducials

Seventeen articles were found that report the experience of 583 patients who have had between 1,004 and 1,797 fiducial markers placed percutaneously into lung tumors or lung tissue near tumors, the first experience reported in 2003. These are summarized in Table 39.3. Follow-up of these patients was from 1 day to 36 months. By far, the most common complication was pneumothorax, with 79 (18 %) patients developing pneumothorax that was large and severe enough to require placement of a chest tube. Only 1 case of pneumonia, 2 cases of grade 5 pneumonitis, and 22 cases of grade 1–3 pneumonitis were reported.

Bronchoscopically Implanted Fiducials

Eleven articles reporting on 236 patients who had 658 fiducial markers placed bronchoscopically in or near peripheral tumors; the first experience reported 8 years ago in 2002. These are summarized in Table 39.2. These patients had primary lung cancer with stages ranging from IA to IV and/or cancer metastatic to the lung and represent some of the most medically compromised patients that are treated for lung cancer. None of them were surgical candidates either because of the (1) stage of the tumor, (2) the severity of their underlying comorbidities, or (3) refusal to undergo surgery. For those patients with lung function reported, FEV_1 was only 30–50 % of predicted. Two pneumothoraces occurred following placement of fiducials in these patients. Follow-up ranged from 1 day to over 16 months. When fiducial migration was occurred 19 % of the time. No cases of pneumonia related to fiducials placed into small airways were reported.

Unfortunately, the literature does not contain significant details regarding the accuracy of fiducial placement with respect to the targeted tumor nor sufficient data to draw any conclusions about long-term survival following treatment when radiation therapy is provided with internal fiducials versus no fiducials or when fiducials are placed by bronchoscopy versus percutaneous.

Summary

The ideal radiation treatment for cancer would deliver a lethal dose of radiation to the entire tumor while simultaneously minimizing radiation dose delivered to surrounding tissues. Technologic advances in imaging and radiation delivery have enabled relatively precise determination of the size and shape of the tumor and the delivery of a tightly focused dose of radiation to a volume of tissue that can be contoured to match the shape and size of a tumor. When this focused and contoured volume of irradiated tissue is coincident with the actual tumor target, then the ideal radiation treatment has been approximated.

Fiducial markers act as visible surrogates of tumor location, and they can provide accurate localization and tracking of tumors, even when the tumor is difficult to see on fluoroscopy or CT scan. A wide variety of fiducials with an equally wide range of shapes, sizes, and surface treatments are currently available for use in the body. Some basic guidelines to follow when implanting fiducials include the following: 4–6 should be implanted to so that three remain in place, they should be placed in and around the tumor such that the bulk of the tumor is bracketed by the fiducials, those placed outside the tumor should be placed as close to the edge of the tumor as possible, and they should not be placed collinearly. By selecting the appropriate fiducial, implantation in the lung and in accordance with these guidelines can be achieved transthoracically or bronchoscopically using a variety of imaging guidance techniques.

Additionally, in the current indexed literature, 583 patients have had more than 1,004 fiducial markers placed percutaneously and 236 patients who had 658 fiducial markers placed bronchoscopically in or near lung tumors. With the exception of a relatively high (17 %) rate of pneumothorax requiring chest tube placement following transthoracic placement, fiducial placement appears quite safe with a low (0.5 %) rate of pneumothorax requiring a chest tube following bronchoscopic fiducial placement and no pneumonias related to the fiducials reported with either implantation technique. Unfortunately, this literature does not contain sufficient data to draw any conclusions about long-term survival following treatment when radiation therapy is provided with internal fiducials versus no fiducials or when fiducials are placed by bronchoscopy versus percutaneous needles.

Table 39.3 Summary of the all published literature on the clinical experience with percutaneously placed fiducial markers in and around lung tumors. Patients did not undergo surgery because of tumor stage; existing comorbidities such as old age, poor respiratory, cardiac, and renal function; or refusal to undergo surgery

Author year	Patients	Stage	Type	Total number or each	Location	Migrated	PTX#	PNA&	Use of fiducial	Follow-up	Time to local progression	Mortality	Comments
Pennathur 2009	100	– and mets	–	1–4 each	Parenchyma and tumor	–	26/100*	–	CyberKnife	20 months (median)	22 months (median)	50 % at 24 months	Pneumonia rate not reported
Pennathur 2009	21	I	–	1–4 each	Parenchyma and tumor	–	10/21*	–	CyberKnife	12–43 months	12 months (median)	10/21	Pneumonia rate not reported
Brown 2009	31	I	Cylinder	31	Tumor	–	–	–	CyberKnife	24–53 months (median)	–	17 % at 4.5 years	Four patients developed grade I-II pneumonitis No pneumothorax requiring hospitalization
Kothary 2009	44	– and mets	0.8–mm cylinder	3–7 each	Tumor	4/-	20/44, 7/44*	–	CyberKnife	1 day	–	0/44	Eight patients had pulmonary hemorrhage
Collins 2007	24	I and mets	0.8–1.0-mm cylinder	3–5 each	Parenchyma and tumor	–	7/24, 4/24*	0/24	CyberKnife	6–30 months	–	17 % at 12 months	Close pulmonary follow-up with frequent PFTs and CT scans Two patients developed grade III pneumonitis
Kupelian 2007	15	I	0.7-mm coil	15	Parenchyma and tumor	0/15	8/15, 6/15*	–	Setup	37–170 days	–	–	No comment on long-term complications. Based on CT scans, no infiltrate seen on first and last CT scan near the fiducial
Yousefi 2007	48	– and mets	Cylinder	221	Parenchyma and tumor	–	16/48, 6/48*	–	–	1 day	–	0/48	Biopsy performed before 23 % of fiducial placements Two patients with hemoptysis; 1 hospitalized One patient with pulmonary edema
Brown 2007	19	IA	–	–	Tumor	–	–	–	CyberKnife	3–21 months	–	4/19	One patient had fiducial placed bronchoscopically Three patients developed grade I pneumonitis
Brown 2007	59	I	–	61	Tumor	–	–	–	CyberKnife	1–33 months	–	8/51	Four patients with grade 1, 2, or 3 pneumonitis No report of pneumonia during follow-up None of the deaths were reported as pneumonia
Pennathur 2007	32	I–V and mets	–	1–4 each	Parenchyma and tumor	–	9/32*	1/32	CyberKnife	9–36 months	11 months (median)	50 % at 26 months	One death related to pneumonia. It is not reported if this was associated with the fiducial

(continued)

Table 39.3 (continued)

Author year	Patients	Stage	Type	Total number or each	Location	Migrated	PTX[#]	PNA[&]	Use of fiducial	Follow-up	Time to local progression	Mortality	Comments
Brown 2007	95	I and mets	–	–	Tumor	–	5/95*	–	CyberKnife	–	–	–	One patient had cardiac arrest during fiducial placement. Three patients developed grade I-II pneumonitis and one developed grade III pneumonitis Many of these patients reported elsewhere by Brown
Muacevic 2007	15	– and mets	–	15	Tumor	–	2/15*	–	CyberKnife	–	–	–	One patient developed grade I pneumonitis One patient developed nausea
Nuyttens 2006	10	I–IV and mets	0.9-mm cylinder and vascular coil	34	Parenchyma and tumor	–	0/10	0/10	CyberKnife	2–11 months	–	0/10	No patients had "shortness of breath" and presumably no pneumonia
Willoughby 2006	11	–	0.7-mm coil	11	Tumor	0/11	3/11	–	Gating	32–51 days	–	–	No comment on longer term complications
Wurm 2006	3	I and mets	0.75-mm coil	3	Tumor	–	0/3	0/3		12–21 months	–	0/3	"…none of the patients developed any toxicity"
Le 2006	32	I and mets	–	3–5 each	Tumor	1/-	6/32, 3/32*	–	CyberKnife	9–32 months	~16 months (median)	3/32	Four patients with grade 2 or 3 pneumonitis at 3–6 months Two patients with grade 5 pneumonitis at 5 months
Whyte 2003	23	– and mets	1.0-mm cylinder	2–4 each	Parenchyma and tumor	–	3/23, 1/13*	–	CyberKnife	1–26 months	–	4/23	No patients developed radiation pneumonitis, no reported pneumonia

 # PTX pneumothorax, *& PNA* pneumonia, * pneumothorax requiring a chest tube, "–" indicates not reported

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Management of Subglottic Stenosis and Subglottic Stenosis in Systemic Disease

40

António Bugalho

Introduction

The management of central airway obstruction is a common problem for the interventional pulmonologist. In contrast, subglottic stenosis (SGS) remains a relatively rare condition, however one of the most demanding and challenging to treat.

The subglottic airway is a vulnerable site for symptomatic stenosis because it is one of the narrowest regions of the respiratory tract and is formed by a complete nonexpandable ring. When SGS is identified, a wide range of treatments can be proposed. The therapeutic process involves a selection between conservative, endoscopic, and surgical procedures, but the results are not always satisfactory. A multidisciplinary approach is usually recommended, as the decision for a specific intervention is dictated by the needs of each patient and demands a high degree of expertise and collaboration among interventional pulmonologists, thoracic surgeons, and otolaryngologists.

According to the etiology and severity, a combination of endoscopic tools and techniques can be applied to successfully manage SGS. In most cases, these minimally invasive procedures are able to provide good treatment outcomes, in this high morbidity condition.

Subglottic Definition and Anatomy

SGS is a congenital or acquired narrowing of the subglottic airway. Advanced knowledge of the larynx anatomy, configuration, size, and proportions is of major importance to all interventional physicians, in order to correctly manage SGS (see Chap. 11 on Airway Anatomy). Briefly, the precise anatomic boundaries of the subglottic area, in the craniocaudal direction, are defined by the inferior arcuate line of the vocal cords – transition of squamous epithelium to high columnar respiratory epithelium – to the lower margin of the cricoid cartilage. In the lower horizontal plane, the full-term neonate has a subglottic diameter of 4.5–5.5 mm, and in adults, the mean diameter of the cricoid is 17 mm in males (range 13–23 mm) and 13 mm in females (range 11–19 mm). Disruption of the normal gross anatomy and tissue architecture of the subglottis is prone to reduce lumen circumference and create a significant obstruction (Fig. 40.1).

Etiology and Pathogenesis

During the first decades of the twentieth century, infection and external airway trauma were the primary causes for SGS. In the late 1960s, the incidence of acquired SGS began to increase as a result of long-term intubation and other invasive procedures of the airway. Currently, common etiologies resulting in SGS are endotracheal intubation, tracheotomy, previous airway surgery, neoplasms, and radiation for oropharyngolaryngeal tumors. Other causes, while rare, are important to consider when evaluating SGS of unclear etiology (Table 40.1).

SGS can be classified as congenital and acquired. The acquired form is much more frequent than the congenital type and can be subdivided into traumatic, inflammatory, infectious, and tumoral. An additional inadequately characterized female population suffers from idiopathic SGS (ISGS).

Congenital SGS

Even though this type of stenosis is uncommon, it is the third most frequent congenital airway problem. A malformation of the cricoid cartilage is linked to inadequate recanalization of the laryngeal lumen upon conclusion of the normal epithelial fusion at the end of the third month of gestation.

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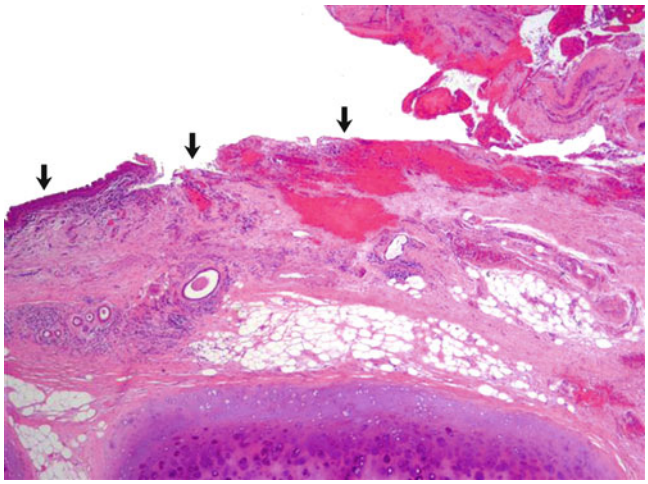

Fig. 40.1 Injured subglottic airway displays mucosal ulceration and incomplete reepithelialization (*arrows*) with hemorrhagic areas and collagen deposition. This altered healing process may lead to airway stenosis

Table 40.1 Causes for subglottic stenosis

Congenital	Membranous
	Increased fibrous connective tissue, hyperplastic submucous glands, granulation tissue
	Cartilaginous
	Cartilage deformity (small or elliptical cricoid, large anterior or posterior lamina, generalized thickening, submucous cleft), trapped first tracheal ring
	Combined stenosis
Acquired	Trauma
	Post-intubation, previous airway surgery (high tracheotomy, percutaneous tracheotomy, cricothyroidotomy, prior surgery), accidental (foreign body, thermal, or caustic inhalation, radiation, blunt, or penetrating trauma)
	Infection
	Tuberculosis, syphilis, leprosy, diphtheria, bacterial tracheitis, croup, typhoid fever, scarlet fever, laryngeal scleroma
	Inflammatory and autoimmune diseases
	Wegener's granulomatosis, relapsing polychondritis, amyloidosis, sarcoidosis, systemic lupus erythematosis, inflammatory bowel disease, gastroesophageal reflux
	Tumor
	Carcinoma, hemangioma, papilloma
Other	Idiopathic subglottic stenosis

Different degrees of atresia, stenosis, or webbing can be found in these patients (Fig. 40.2). Histopathologically, congenital SGS can be subdivided into cartilaginous and membranous. The cartilaginous type results from a thickened or distorted cricoid cartilage, creating an anterior subglottic shelf that extends to the posterior region. It is frequently more severe than the membranous stenosis and is rarely managed successfully with endoscopic techniques. The membranous form is more common, circumferential, often involving the true vocal cords, and is characterized by fibrous soft tissue thickening.

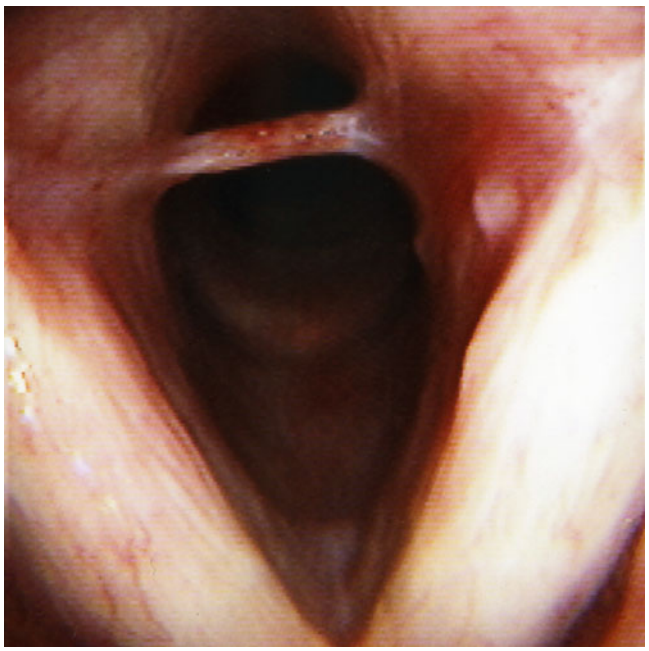

Fig. 40.2 Congenital subglottic web with Myer-Cotton grade I cricoid cartilage stenosis. This thin web was mechanically broken

Laryngeal Trauma

Trauma is the most frequent cause of acquired laryngeal stenosis in children and adults. Internal subglottic trauma is usually iatrogenic (e.g., endotracheal intubation, tracheotomy, or prior tracheal instrumentation). External trauma can be originated by contusion, penetrating wound, or inhalation injury.

In SGS caused by intubation, several risk factors have been identified such as prolonged intubation, large-caliber endotracheal tube, traumatic intubation, numerous re-intubations, local infection while intubated, frequent displacement of the endotracheal tube, and the concomitant existence of a nasogastric tube (Fig. 40.3a). The pathogenesis of this form of acquired SGS is not fully understood. The more widely accepted theory proposes that high pressure from a tube or cuff exceeds the capillary pressure of the airway wall and contributes to ischemia of the mucosa and cartilage (Fig. 40.3b). The three overlapping phases of wound repair are inflammation (initial injury generates edema and vascular congestion with recruitment of cells and mediators, occasionally ulceration and infection can occur), proliferation (reepithelialization, neovascularization, increased fibroblast activity, granulation tissue), and airway remodeling (collagen deposition, scar formation, contracture, and loss of structural integrity leading to stenosis).

Postsurgical SGS may occur as a complication of previous tracheotomy, percutaneous tracheotomy, cricothyroidotomy, and surgical treatment for airway neoplasms.

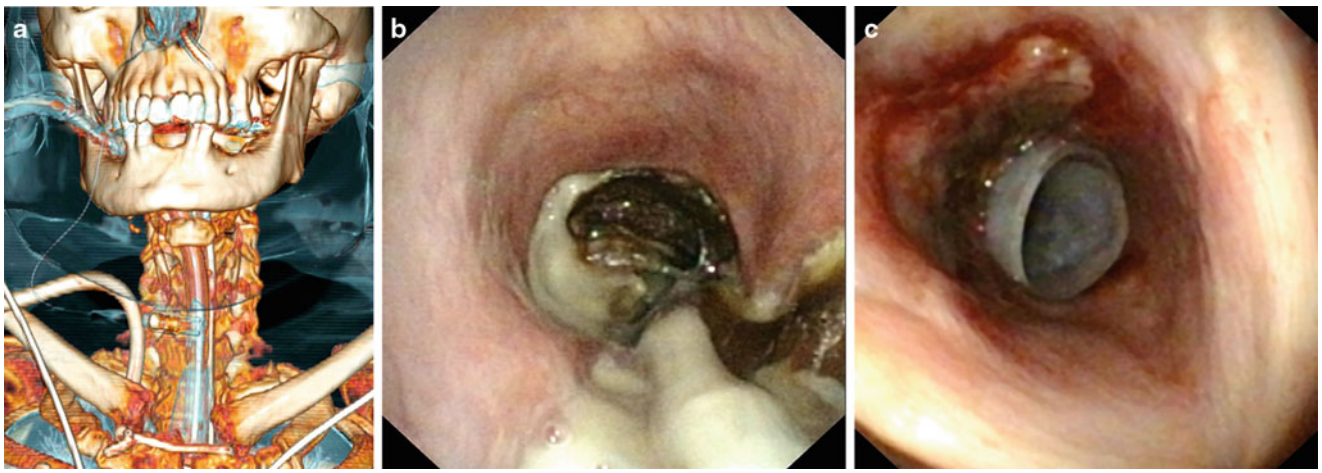

Fig. 40.3 CT reconstruction of a 78-year-old female with subglottic stenosis caused by prolonged endotracheal intubation (**a**). Multiple comorbidities, high position of the tube, excessive cuff pressure, and the presence of a nasogastric tube contributed to an extensive mucosal and cartilage damage (**b**). A straight silicone stent 12/40 mm was deployed (**c**)

Stenosis following tracheotomy may be above the stoma, at the same level as the stoma, at the cuff site, and at the tip of the cannula. In addition to ischemic mucosal injury and chondritis, fracture of the cartilage is an important factor for SGS in these patients. Damage to the cartilage above the stoma is the most frequent cause of stenosis after emergency tracheotomy performed with a poor technique.

The incidence of traumatic SGS can be radically reduced if high tracheotomy and cricothyroidotomy are only performed in extreme emergencies; aggressive endoscopic manipulation for benign laryngeal lesions is avoided; intubation and endoscopy are done gently on calm patients; factors contributing to laryngeal trauma secondary to intubation are recognized and prevented when possible.

Infection

Acute laryngotracheobronchitis, an acute viral respiratory disease commonly seen in children, can cause subglottic narrowing. Croup most commonly occurs in children 6–36 months of age, and it is rare beyond the age of 6. Acute bacterial tracheitis can also originate thick, purulent secretions and mucosal edema that may cause symptoms of upper airway obstruction.

SGS secondary to chronic infection is rare, except in certain endemic geographic areas, and it has been described in patients with tuberculosis, syphilis, diphtheria, typhoid fever, scarlet fever, leprosy, and laryngeal scleroma.

Though infrequent, subglottic and endotracheal tuberculosis may result in significant obstruction related to the initial lesion or subsequent stricture formation. Some degree of stenosis may still develop despite appropriate antituberculosis chemotherapy.

Laryngeal scleroma is also an uncommon chronic disease originated by an aerobic gram-negative bacteria, *Klebsiella rhinoscleromatis*. It is prevalent in certain regions such as Africa, Asia, Central and South America, and Central and Eastern Europe. It typically involves the nose but can also affect other parts of the respiratory system. Subglottic involvement is reported in 23% of cases. Following the initial infection, three sequential phases are described: exudative stage, with active inflammation, edema, congestion, and necrosis; proliferative stage characterized by multiple reddish nodules; and fibrotic stage with cicatricial tissue. Clinical suspicion is important in order to achieve the diagnosis. The CT scan normally shows concentric irregularities and narrowing in the subglottic space. Biopsy specimens are needed for the definitive diagnosis, usually obtained during the proliferative phase. There is a recognizable histological pattern with clusters of vacuolated histiocytes – Mikulicz cells. Treatment should be directed according to clinical stage, severity, and anatomic location. In the proliferative phase, long-term antibiotics are the treatment of choice. In the fibrotic stage, if the patient is symptomatic and there is mild subglottic involvement, endoscopic procedures can be valid therapeutic options. Open surgical techniques have been attempted for extensive SGS.

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a multisystemic disease characterized by necrotizing vasculitis and granuloma formation that has a predilection for the upper and lower respiratory tracts and kidneys. Its etiology is unknown and affects both males and females with a peak around 40–55 years old. The course of WG varies widely, from localized to multisystemic, from mild to life-threatening disease. Nasal and sinus findings are present in a high percentage of cases (e.g., chronic sinusitis, epistaxis, septal perforation, saddle nose deformity). SGS may occur either as a presenting characteristic or as a

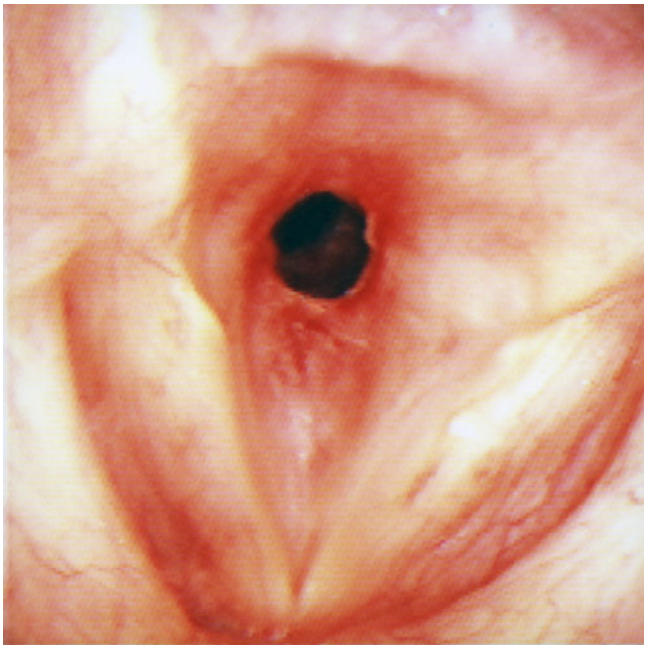

Fig. 40.4 Subglottic stenosis in Wegener's granulomatosis. One can notice the red inflammatory friable tissue circumferentially narrowing the subglottis

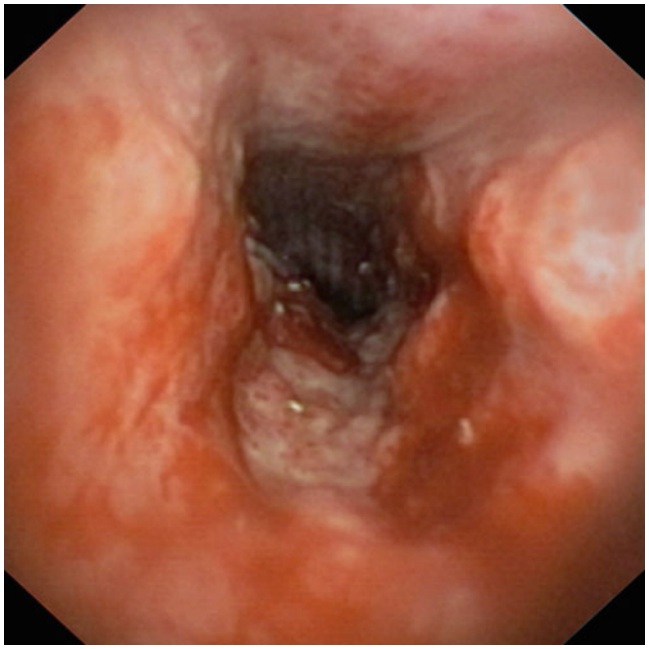

Fig. 40.5 Bronchoscopic appearance of laryngotracheal amyloidosis in a 37-year-old female patient. Amyloid deposits infiltrate the mucosa reducing airway caliber

late-stage manifestation of the disease and is reported in 12–23% of WG patients (Fig. 40.4). It often occurs independently from other features of disease activity and frequently does not improve with systemic treatment. Laboratory studies may show a positive anti-neutrophil cytoplasmic autoantibodies (ANCA-c) test, although it should be interpreted cautiously because ANCA-c may be positive in other diseases and WG may be present in face of a negative ANCA test. Chest radiographs and CT scans may show pulmonary infiltrates and/or cavitary nodules. Biopsy remains the gold standard for the diagnosis, but specimens from the larynx and trachea often do not exhibit the characteristic inflammatory infiltrates with multinucleated giant cells, granuloma formation, and vasculitis of the small and medium vessels. Systemic immunosuppressive therapy is the mainstream treatment in WG. The endoscopic management of subglottic lesions (laser resection, serial dilatations, topical corticosteroids, local mitomycin-c) is an important aspect in those who remain symptomatic despite appropriate medical management.

Amyloidosis

Amyloidosis is a disorder characterized by extracellular tissue deposition of fibrillar proteins and can involve virtually any organ or system. It can be idiopathic or associated to inflammatory, hereditary, or neoplastic diseases. Respiratory tract amyloidosis may be part of a widespread or local process. Sites in the larynx that show predilection for nodular or polypoid amyloidosis include the ventricles, false cords, aryepiglottic folds, and the subglottis. Pulmonary manifestations comprise tracheobronchial infiltration, persistent pleural effusions, and parenchymal nodules. There may be diffuse narrowing and wall thickening, circumferential airway involvement, often with ossification of the amyloid deposits (Fig. 40.5). Bronchoscopy displays multiple plaques or localized tumor-like masses. Tissue biopsy stained with Congo red and examined under polarized light shows the characteristic submucosal extracellular deposits of amyloid protein that confirms the diagnosis. Bronchoscopy-based techniques (laser therapy, stenting) have been suggested as a possible method for dealing with subglottic obstructing lesions. There is no effective medical treatment and excision, when possible, remains the treatment of choice in localized forms of amyloidosis.

Relapsing Polychondritis

Relapsing polychondritis (RP) is a multisystemic immune-mediated disease characterized by recurrent episodes of inflammation of cartilaginous structures. RP is most likely between age 40 and 60, although it can occur in younger patients. One-third of cases develop in association with another recognizable condition, particularly systemic vasculitis or connective tissue diseases. Auricular chondritis represents the usual initial presentation, but the disease may involve the nose, laryngotracheobronchial tree (malacia and/or stenosis),

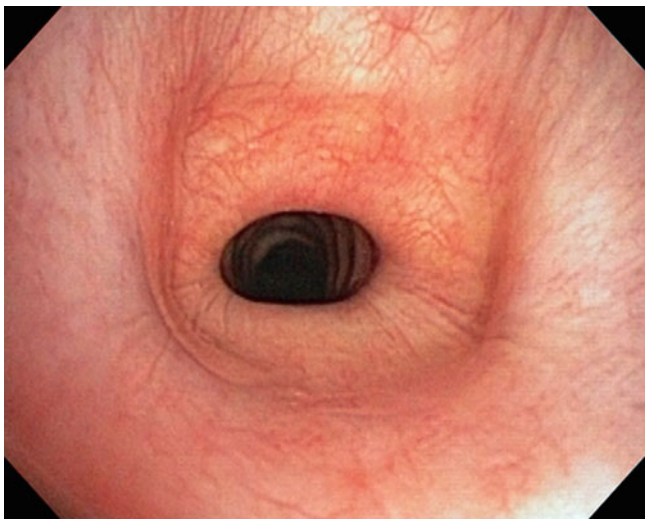

Fig. 40.6 Firm thickening of the subglottis in a patient with relapsing polychondritis (Courtesy of Armin Ernst, M.D.)

peripheral joints, and other organs. In the active stage, there is a red, warm, painful swelling of the cartilage. After the inflammatory episode, significant destruction may occur. The definitive diagnosis is based on the presence of three of the following criteria or at least one along with a confirmatory biopsy showing inflammatory changes in the cartilage: recurrent bilateral auricular chondritis, nonerosive inflammatory polyarthritis, nasal cartilage chondritis, ocular inflammation, respiratory tract chondritis, and cochlear or vestibular damage. CT and bronchoscopic findings include diffuse smooth thickening of the larynx, trachea, and proximal bronchi; thickened, densely calcified cartilaginous rings with spared posterior tracheal membrane; tracheal wall nodularity; diffuse narrowing of the tracheobronchial lumen, major airway collapse caused by destruction of cartilaginous rings (Fig. 40.6). It is difficult to predict the clinical path of the disease because it can have an indolent course or fulminating consequences. This means that it is important to perform a prompt diagnosis and treatment plan before irreversible damage occurs. Medical management of RP focuses on suppressing the acute inflammatory process. Ernst and coworkers have shown that it is feasible to treat these patients by endoscopic procedures (dilatation, stenting). The majority experience improvement of respiratory symptoms although on occasion, involvement of glottis and subglottic regions may necessitate a tracheotomy.

Tumor

Direct extension of a locally advanced tumor and/or extrinsic compression may cause SGS (e.g., laryngeal cancer, thyroid tumors). Primary laryngeal and tracheal tumors are extremely rare in children, with papillomas, hemangiomas, and granular cell tumors being the most common. In adults, squamous cell carcinomas followed by adenoid cystic carcinomas are the most frequent and in some instances may cause SGS. Other less common tumors in adult patients include hemangiomas, neurogenic tumors, and papillomas.

Recurrent papillomatosis results from infection of the upper respiratory tract by the human papilloma virus (HPV). HPV6 and 11 are most commonly involved, while HPV16 has been reported and may be associated with an increased risk of malignant degeneration. This disease is most common in children but may also occur in adults, as previously stated. Infection frequently occurs during birth, and laryngeal papillomas may lead to contamination of the trachea and lungs. At bronchoscopy, the papillomas have a polypoid appearance and may involve the larynx, trachea, or bronchi (Fig. 40.7). Endoscopic interventions are crucial since repeated treatment is usually required because recurrence is quite common.

Idiopathic Subglottic Stenosis

ISGS is a rare inflammatory process of unknown cause, usually limited to the subglottic region and the first two tracheal rings. It is an exclusion diagnosis based on the absence of recent intubation or trauma, and other rare diseases that can affect the subglottis. Some reports advance a hormonal cause, since most patients are females with preponderance in the 20–50 age range, although no major causal factor was identified. Mark et al., in 63 tracheal resections performed in patients with the diagnosis of ISGS, found an extensive fibrosis, dilation of mucus glands, a relatively normal cartilage, and in most cases, a positive staining for estrogen and progesterone receptors in fibroblast cells. The theory of laryngopharyngeal reflux as a possible etiological factor seems to be excluded by recent reports given the poor responses to anti-gastroesophageal reflux medication. A new hypothesis suggests that severe coughing episodes may cause mechanical trauma, intermittent disruption of blood supply to the cricoid, and scarring in the subglottic area leading to ISGS. Dilatation, laser incisions, intralesional steroids, mitomycin-c, and airway stenting have all been used for the initial management of ISGS.

Other Causes

Gastroesophageal reflux has been proposed as a medical condition that may exacerbate the pathogenesis of SGS, be the single cause for stenosis, or cause restenosis after repair. Roh and colleagues have induced subglottic injury in a rabbit model demonstrating that the inflammation scores, fibrosis, thickening, and luminal stenosis were greatest in the acid

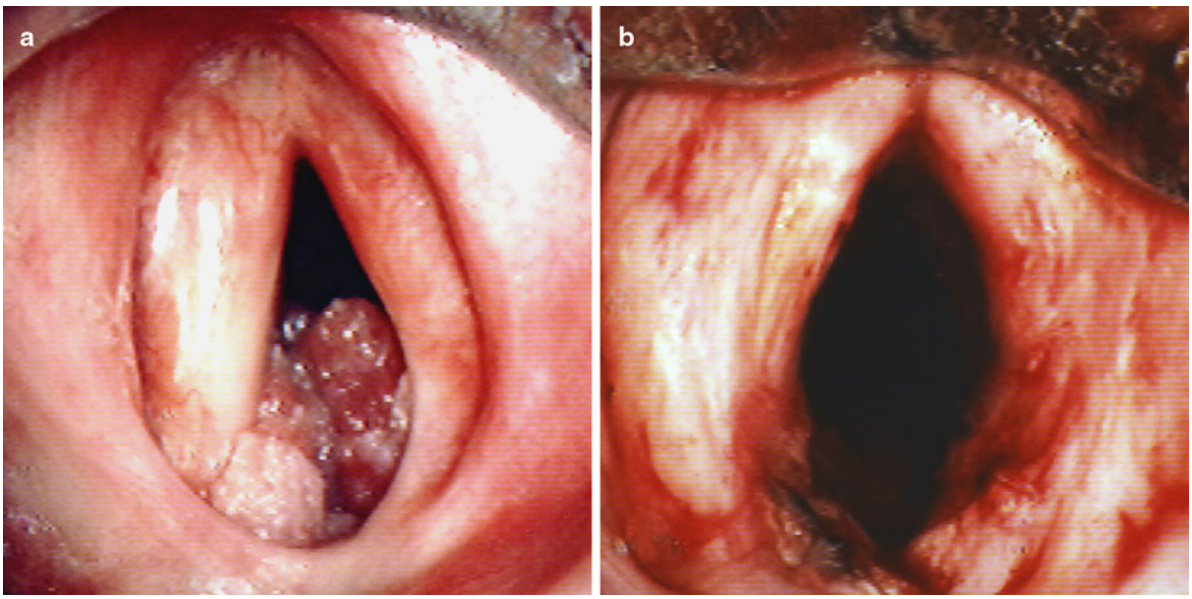

Fig. 40.7 Glottic and subglottic cauliflower-like tumors with smooth surface corresponding to recurrent papillomatosis in a 42-year-old (**a**). There was a marked improvement in airway caliber after laser treatment (**b**)

reflux group compared to the nonacid reflux group, suggesting that subglottic wound healing is significantly affected by acidic conditions. Active empirical treatment is recommended for this condition in patients undergoing SGS treatment.

Additional systemic factors may also increase the risk of subglottic injury and decrease the rate of wound healing (e.g., diabetes mellitus, immunodeficiency, and chronic infections).

Diagnosis and Pre-interventional Assessment

SGS is generally suspected based on the clinical findings. Congenital SGS usually occurs in very early life with symptoms of airway distress and laryngeal involvement: feeding abnormalities, stridor, abnormal or absent cry, and hoarseness. If the stenosis is severe, the neonate will present major respiratory distress at birth. Congenital SGS is often associated with other malformations, and the presence of further causes for respiratory compromise should always be assessed. Adults with mild congenital stenosis are usually asymptomatic and are diagnosed after a difficult intubation or while submitted to bronchoscopy for other reasons (Fig. 40.2).

In acquired SGS, frequently, there is a history of prior intubation with symptoms of progressive dyspnea, biphasic stridor, and functional limitations, depending on the severity of stenosis. Early manifestations may be mistaken for other diseases (e.g., asthma, COPD). Sometimes, SGS may present as a patient in the intensive care unit who fails extubation. It is mandatory to review the characteristics of previous intubations: date, duration, size of the endotracheal tube, number of subsequent intubations, and if any intubations were traumatic. If laryngeal trauma is not the cause, other etiologies should be investigated and eliminated; otherwise, disease recurrence may lead to repeated treatment failures. A complete clinical exam should be performed in all patients since many of the previous-mentioned diseases may have systemic repercussions.

Careful pre-interventional evaluation is essential to obtain good results. Flow-volume loops provide some information regarding the level (e.g., extra- vs. intrathoracic) and degree of obstruction (e.g., mild vs. severe). They allow comparing post-interventional results with pre-interventional values, in order to assess therapeutic effectiveness. The Medical Research Council scale is also an approved instrument to evaluate the degree of dyspnea and treatment efficacy in SGS patients. Standard neck and chest radiographs with antero-posterior and lateral views of the subglottic and tracheal air column are still useful, especially in children. They have been gradually replaced by high-resolution CT and magnetic resonance imaging (MRI) because these modalities offer detailed information of the airway and adjacent structures; are able to assess size, location, and extent of airway lesions; and show areas beyond high-grade stenotic segments (Fig. 40.8).

The technological improvements in CT and MRI have not substituted bronchoscopy as the primary procedure for the diagnostic workup and pre-interventional assessment. Flexible bronchoscopy is an effective method for gathering preliminary information prior to any interventional attempts. It allows the detection of supraglottic/glottic and subglottic abnormalities, length and severity of stenosis, evaluation of vocal cords mobility, distance from the vocal cords,

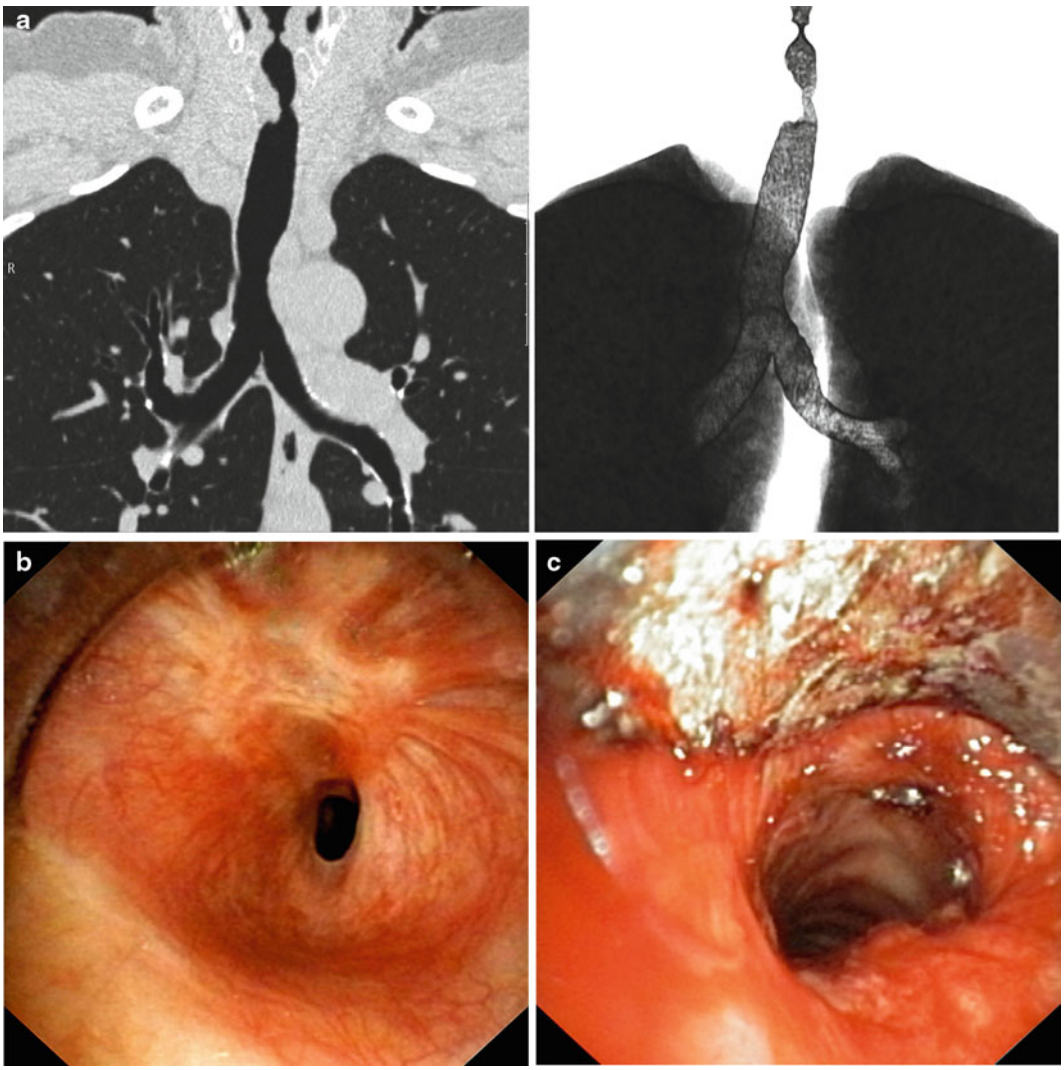

Fig. 40.8 CT coronal image and 3D reconstruction of a patient with >1-cm-length idiopathic subglottic stenosis (**a**). Bronchoscopy revealed a complex stenosis, Myer-Cotton grade III (**b**). Nd:YAG laser radial incisions followed by balloon dilatation restored airway lumen (**c**)

Table 40.2 Subglottic stenosis classification systems

	Myer-Cotton	McCaffrey	Lano
Grade/stage I	<50% obstruction of the lumen	Subglottic or tracheal lesion <1 cm long	Lesion involves one subsite (glottis, subglottis, or trachea)
Grade/stage II	51–70% obstruction of the lumen	Lesion confined to the subglottic area >1 cm	Lesion involves two subsites
Grade/stage III	71–99% obstruction of the lumen	Subglottic and tracheal lesions not involving the glottis	Lesion involves all three subsites
Grade/stage IV	100% obstruction of the lumen	Glottic involvement	

assessment of cartilage involvement, and degree of scar maturity. One should always examine the tracheobronchial tree for secondary lesions and the suprastomal area if the patient has a tracheotomy or a tracheotomy is planned. Rigid bronchoscopy under general anesthesia allows a more accurate and reliable measurement of the length and diameter of the stenotic airway and is ideal to plan appropriate treatment. The introduction of sequentially larger endotracheal tubes has been used to assess the degree of SGS. Caution should be taken with this method as it may induce further iatrogenic injury to the airway.

In order to predict interventional success, several laryngotracheal stenosis classifications were proposed (Table 40.2). The Myer-Cotton system applies to firm circumferential

stenosis confined to the subglottis with four staging degrees based on the percentage of reduction in cross-sectional area. It must be emphasized that this classification has some limitations since it has been applied to all laryngotracheal stenoses and relies on the interventional pulmonologist skills and judgment. McCaffrey suggested that treatment success depends on the subsites involved and length of the stenosis, but it does not take into account the degree of luminal reduction. Lano and coworkers proposed a method based on the number of subsites implicated (glottis, subglottis, and trachea) and degree of stenosis to better predict patient prognosis dictated by successful decannulation and absence of disease recurrence. They reported a negative correlation between management success and the number of sites affected.

As a rule, stage I lesions have the highest success rate while stage IV lesions have the lowest. Because no staging system permits a true comparison of patients, treatment modalities, and outcomes among different centers, Freitag and colleagues proposed a new classification of central airway stenosis based on the type, degree, location, and transition zone. Further studies are needed to confirm the usefulness of this system, particularly in SGS.

SGS may also be classified according to the morphological aspects in simple or complex stenosis, with management and prognostic repercussions. The simple stenoses comprise weblike, short segment (<1 cm), membranous concentrical, without cartilage damage lesions. Complex stenoses are characterized by an extensive endoluminal occlusion (≥1 cm), circumferential contraction scarring, and/or associated malacia or loss of cartilaginous support and have a lower endoscopic treatment success rate compared to simple stenoses.

Management

The primary goals in treating any patient with upper airway obstruction are assurance of adequate oxygenation, ventilation, and management of the underlying condition. Treatment must be individualized according to the pathologic findings and the patient's health status. Different management possibilities include observation, systemic drug therapy, local drug therapy, intubation/reintubation, tracheotomy, endoscopic treatment, and open surgical management. Each patient requires a therapeutic plan that includes one or a combination of these modalities. A multidisciplinary approach incorporating medical and surgical specialists is applied in many centers.

Whenever identified, medical causes must be addressed (e.g., appropriate control of infections, treatment of inflammation in WG, gastroesophageal reflux management). In early stenosis, systemic corticosteroids were generally prescribed, but there is insufficient data to recommend the use of these drugs in all SGS cases.

A minimal symptomatic adult patient with stable nonprogressive SGS, without limitations of quality of life, may be successfully managed with close observation. In a child with mild stenosis, conservative treatment, regular follow-up, and anticipation of growth may also obviate the need for further therapy.

Endoscopic modalities may constitute the first option for short segment, membranous, benign, concentric not involving the cartilage SGS; for preservation of a safe airway while waiting for other treatments; and for treatment/palliation of symptoms for patients who are not surgical candidates due to the stenosis characteristics (e.g., extensive laryngotracheal stenosis), active local infection, major inflammatory state, poor general medical status, and unstable coexistent diseases. They are also used to treat restenosis following open reconstructive procedures. Success rates for primary endoscopic treatment of SGS vary in the literature between 40% and 94% depending on the severity of stenosis and appropriateness of the indication. Myer-Cotton grade I stenoses are usually successfully managed endoscopically. Grade II and III lesions presenting as weblike diaphragms without loss of cartilage support represent good indications for an endoscopic treatment trial. From grade I to grade III, the endoscopic management success rate decreases from 100% to 76% and the number of interventions needed for treatment increases. In moderate to severe cases of congenital and acquired SGS (grades III and IV), only a small percentage of cases will be successfully managed by endoscopic methods. When the cartilaginous framework of the larynx is significantly damaged, most patients require a tracheotomy to establish a safe airway and reconstructive repair.

Factors associated with high endoscopic failure are circumferential scarring; fibrotic scar tissue in the interarytenoid area of the posterior commissure; severe bacterial infection of the trachea; exposure of perichondrium or cartilage during laser excision, predisposing to perichondritis and chondritis; combined laryngotracheal stenosis; failure of previous attempts at endoscopic repair; vertical scar length >1 cm; and significant loss of cartilaginous support.

The more commonly used endoscopic therapeutic options include dilatation, laser tissue resection with or without local mitomycin-c or corticosteroids, and airway stenting. WG is a paradigm for SGS management. In a symptomatic WG patient, the presence of a fixed localized SGS usually requires more than systemic treatments, and this includes all the above mentioned, individually or combined.

Since the early years of interventional pulmonology, SGS was managed with mechanical dilatation alone using rigid dilators and scopes. However, the process required multiple procedures and had a high recurrence rate. Newer balloon dilatators offer an advantage as dilation can be gentle without shearing the mucosa, aggravating cicatricial stenoses.

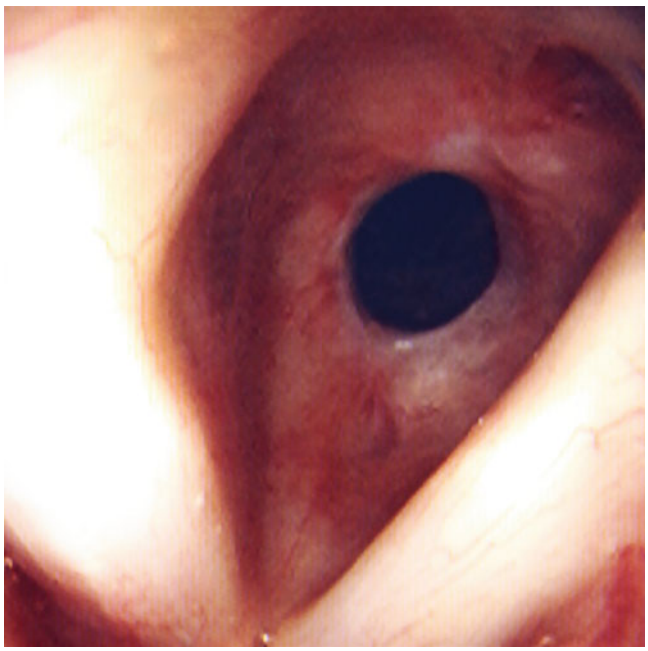

Fig. 40.9 Subglottic restenosis in a Wegener's granulomatosis patient 13 months after reconstructive surgery

This method has been use to treat ISGS and SGS in WG patients, and proved to be effective in the management of soft isolated lesions. In more extensive or firm SGS, there is evidence that endoscopic dilatation alone is relatively ineffective in the majority of cases. However, association with other procedures increases success rates.

A variety of heat techniques have been tested in SGS, including electrocautery and argon plasma coagulation, although some authors argue against these methods since they may cause uncontrolled tissue destruction. It is consensual that the preservation of airway epithelium with minimal trauma is essential for good results. Laser has supplanted other techniques because minimal energy delivered over a short duration allows scar tissue to vaporize without causing significant bleeding or edema and its precision avoids trauma to the normal surrounding areas. The CO_2 laser is a precise cutting tool but has a limited coagulation effect compared to the Nd:YAG laser. The main disadvantage of the Nd:YAG laser is the greater depth of penetration. Operator's inability to control the extent of laser deepness or employ it at all times parallel to the wall may lead to further damage of the mucosa and cartilage.

Many authors have reported good results in treating early or mild subglottic stenosis using CO_2 or Nd:YAG laser, although multiple procedures may be required to obtain the desired result. Cautious technique creating mucosal trapdoor flaps or radial incisions in three or four quadrants can release the constricting stenotic ring and simultaneously preserve islands of intact mucosa between the incisions that allow epithelial restructuring and resurface of the expanded lumen (Fig. 40.9). The combination of this method with gentle dilatation may produce better long-term results, with a 75% success rate in selected cases (short, weblike stenoses). Monnier and colleagues used the CO_2 laser in patients with laryngotracheal stenosis and reported that the improvement to a nearly normal airway declined from 92% for grade I Myer-Cotton classification to 46% for grade II and 13% for grade III stenoses. Based on these findings, a therapeutic algorithm was developed, stating that endoscopic interventions should be attempted first in the presence of SGS grade I/II, stenosis <1.5 cm in a craniocaudal direction, and membranous type with an adequate cartilaginous support. The same conclusions were drawn by Cavaliere et al., who achieved a 66% success rate in post-intubation stenosis patients managed by laser, dilatation, and stent, considering these a safe first-line therapy and reserving selected cases and relapsing stenoses for surgery.

The ways to directly modulate airway wound healing have been under intense investigation, in order to decrease SGS recurrence. Treatments included local corticosteroids, halofuginone, colchicine, tamoxifen, 5-fluorouracil, and mitomycin-c.

Steroids have long been known to affect the curative process and inhibit scar formation and were topically applied in SGS patients without consistent results. Several authors described the use of mechanical subglottic dilatation followed by injection of a long-acting corticosteroid (e.g., methylprednisolone) into the stenotic lesion; however, patients frequently required multiple therapeutic sessions. Hoffman and coworkers reported that WG patients with established laryngotracheal scarring required a mean of four intralesional corticosteroids and dilation procedures at mean intervals of 7 months to maintain patency, but none of the 21 patients necessitated a new tracheotomy. The best results were obtained when these endoscopic techniques were carried out prior to other forms of surgery which may lead to increased cicatricial tissue.

Although controversial, mitomycin-c has been routinely used after laser and/or dilatation with alleged positive results. Mitomycin-c inhibits fibroblast proliferation and activity, improving the patency rate and decreasing scar development. It is usually placed on a cottonoid pledget with a concentration of 0.4 mg/ml and topically applied to the area of laser excision of subglottic scar. The length of application varies from 2 to 3 repeat applications of 2 min each to a single application of 4–5 min. In 2010, Veen and Dikkers performed a literature review for side effects of mitomycin-c in the upper respiratory tract. Forty-six articles were retrieved and the authors concluded that topical application of this agent on a wound with consecutive irrigation with saline could be performed safely. One should restrain to use higher concentrations of mitomycin-c as serious complications can occur. Care should be taken to avoid contact with unprotected skin or eyes and follow correct disposal protocols.

Despite the feeling that this antiproliferative agent is helpful, the conclusions of most clinical trials are limited by retrospective design, small populations, or short-term follow-up. These studies also suggest that mitomycin-c may postpone but not prevent the recurrence of symptomatic stenosis in the majority of patients with laryngotracheal stenosis.

In some procedures, additional stenting is an important element of the therapeutic strategy. Possible indications for the use of stents in SGS include post-intubation SGS after failure of laser resection and/or dilation; benign complex stenosis in patients who are not surgical candidates (Fig. 40.3); benign stenosis from inflammatory or infectious processes, while awaiting response to systemic therapy or open surgical resection; restenoses or anastomotic stricture following open surgery; expiratory airway collapse; and extrinsic compression.

When choosing stents for SGS, attention should be given to the material, size, position, and duration of stenting. Most frequently, the preferable option in SGS is to use the rigid scope to deploy a short and wide straight silicone stent followed by inflation of a balloon inserted into the folded stent to obtain complete opening and a more favorable anchoring. The subglottic location of the stenosis sometimes increases the difficulty to correctly position the stent. Once the proximal end of the stent is located in the subglottic region, it may induce ulceration and granulation tissue formation with subsequent restenosis. Ko and colleagues analyzed stent complications, the influence of stent location, and stent-to-vocal-fold distance on the risk of granulation formation in patients treated with Dumon stents and Montgomery T-tubes, below, at, or across the vocal cords. The rate of granulation formation was 63% for procedures with distances of ≤10 mm, 22% for those between 11 and 20 mm, and 11% with ≥20 mm from the vocal cords. A 10-mm distance between the vocal cords and the proximal end of the stent seems to be an acceptable safety margin, whenever possible.

Subglottic stents are prone to distal or proximal migration. This was reported by Martinez-Ballarin and colleagues in 18% of patients treated with Dumon stents for laryngotracheal stenosis. Tracheotomy followed by Montgomery T-tube insertion is occasionally chosen to avoid migration and provide a safe airway. Further indications for Montgomery T-tubes were retrospectively evaluated by Carreta et al. and included treatment of laryngotracheal stenosis patients with a permanent contraindication to surgery, transitory presurgical measure in patients with a temporary contraindication to reconstruction, and treatment of complications of tracheal surgery. In patients with preexisting tracheotomies, Shapshay and colleagues showed that management with laser and T-tube stents may achieve a successful outcome in 67% of cases. However, 75% of these patients required additional treatments over a variable follow-up period of 1–5 years. In selected patients with SGS and malacia who are not candidates for surgical resection, tracheotomy or Montgomery T-tubes, or who have had repeated stent migration, external stent fixation may be performed.

Bronchoscopic supervision is advisable to detect and treat complications as well as to monitor treatment efficacy. In some cases of benign disease, the stent can be removed after several months without symptomatic recurrence or restenosis. Expandable metallic stents must be avoided given the significant long-term complications that are associated with the placement of permanent stents for benign conditions.

New technologies are often introduced to meet the needs of the interventional pulmonologist. Some authors used the microdebrider to resect obstructing tissue in the central airways. This instrument is composed of a metal tube with a rotating blade coupled with suction that can promote a rapid and precise removal of lesions and scar tissue. Although it appears safe in adults and infants, care should be taken to escape inadvertent resection of normal tissue. Further studies are needed in order to compare applicability, efficacy, and safety with other currently available techniques.

There is no standard treatment for all SGS cases or specific diseases causing SGS. Several authors proposed a therapeutic algorithm for optimal management of SGS. Unfortunately, these algorithms are developed as single-center based, with a small number of patients included, short follow-up time, and without comparison between different treatment modalities or valid control groups. Usually, in simple SGS, an endoscopic initial approach is advocated. Open repair is indicated following failure of the conservative efforts, if a more complex stenosis is present or other factors contraindicate this regular approach. In systemic diseases with persistent inflammation, such as WG, more invasive procedures should be performed with extreme caution and aimed at relieving mechanical obstruction since certain surgical modalities have a higher tendency to aggravate the underlying vasculitis and cause restenosis (Fig. 40.9).

One has always to take into consideration that SGS may cause a decrease in the quality of life, but major and repeated procedures itself, if not correctly planed as part of a treatment strategy, may induce additional injury and generate significant morbidity.

Follow-Up

Close post-intervention care and monitoring are essential. In various centers, the post-endoscopic approach involves the use of systemic antibiotics, depending on wound extent and status of the laryngotracheal mucosa, systemic corticosteroids, and active anti-gastroesophageal reflux management, although as previously mentioned, there are no randomized control trials proving the efficacy of these choices.

Wound reassessment is regularly done in the first weeks after procedure (<2–4 weeks) to determine the state of airway

healing, stent position and patency, and the need for further bronchoscopic interventions, since granulation tissue may develop and lead to reobstruction and scarring. Appropriate tracheotomy care is extremely important. In these circumstances, endoscopy is important to assess airway patency and schedule decannulation.

For the first 1–2 years post-intervention, intermittent endoscopy is recommended because it allows long-term evaluation and detection of recurrent stenosis before it reaches a critical stage. In other patients, the duration of the follow-up is determined by the duration of stent placement and of symptoms after stent removal. Any time the patient has airway obstructive symptoms, bronchoscopy should be considered.

Conclusion

SGS is a major medical problem that may cause severe morbidity and life-threatening airway compromise. When SGS is identified, one has to take into consideration the etiology, type of stenosis, its precise location and length, degree of lumen obstruction, patient's health status, and comorbidities. Though good therapeutic options are available, no single medical, endoscopic, or surgical procedure can consistently relieve symptoms and avoid recurrence in all patients. Endoscopic interventions can be used to treat diverse types and grades of SGS. Recent scientific data proves that they constitute the first choice for simple stenoses, whereas complex stenoses often need a multidisciplinary approach and may require surgery.

Current practice is still based on local available resources and equipment, interventional team's training and preferences, and uncontrolled retrospective studies. In the past few years, promising work has been done concerning the treatment of SGS, but many questions remain unanswered. In the near future, a better understanding of the pathophysiology of this condition and the continuous improvement of multimodality approaches and endoscopic techniques will contribute to preventing and treating SGS more effectively.

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Treatment of Airway-Esophageal Fistulas

41

Lutz Freitag

Introduction

Esophago-respiratory fistulas are abnormal communications between the airways and the esophagus causing a spillover of saliva or gastric fluid into the lungs. More than 50% are located in the trachea, followed by the stem bronchi (40%), and a few connect directly to the parenchyma. The etiology is multifactorial. Pediatricians encounter congenital abnormalities that require immediate surgical corrections in the early days of life. It is estimated that 0.04% of babies are born with such a defect. Most fistulas are acquired. Pulmonologists, gastroenterologists, and thoracic surgeons encounter such a clinical condition when they treat cancer patients. In the vast majority (77%), the underlying disease is an advanced esophageal cancer. A quarter of all patients with esophageal cancer have abnormalities between the esophagus and the trachea, half of those develop a visible communication. Another 16% of the acquired fistulas are attributable to lung cancer, and only a few originate from nonmalignant inflammatory diseases such as mediastinitis, tuberculosis, histoplasmosis, traumas, or foreign body aspiration. For many years, the incidence of traumatic fistulas from endotracheal intubation kept growing, but since high-pressure cuffs have been abandoned in the ICUs in the early 1970s, the typical cuff necrosis have become a rare entity. These days, we keep seeing more iatrogenic fistulas from perforations through the posterior membrane into the esophagus after percutaneous dilatation tracheostomies. Other benign acquired fistulas result from extensive neck, larynx, or esophagus surgeries.

The typical clinical signs are coughing associated with food intake, purulent bronchitis, and pneumonia as well as dysphagia. How distressing these symptoms become depends on the size of the fistula. There is a very broad range of clinical presentation. We have recently seen a university student complaining about chronic cough. When taking his history, he reported that he used to impress his classmates with a special trick. He could eat grapes and could cough out the seeds further than his friends could spit them out. Bronchoscopy revealed a small chronic, probably congenital tracheoesophageal fistula. On the other end of the spectrum, we have seen septic patients with huge defects of the posterior membrane into the mediastinum and the esophagus who could only be kept alive by double lumen intubation. It is obvious that there is no universal treatment approach. An individually tailored, multidisciplinary approach is mandatory.

Diagnosis

Occasionally, the diagnosis is made if a barium or gastrografin swallow accidentally outlines the airways. Under normal conditions, the planned diagnostic approach is flexible bronchoscopy followed by gastroscopy. Because of possible side effects, barium swallow cannot be recommended for establishing the diagnosis of a fistula. It is also important to examine the highest part of both tracts. If the patient is intubated, bronchoscopy can be performed through the endotracheal tube, but this device needs to be deflated and pulled out completely over the scope to avoid overlooking very high fistulas. Very small fistulas can be missed if the mucosa is red and swollen. In one case, I could only localize the fistula by pressing against the posterior wall of the trachea with a rigid bronchoscope. Under pressure, whitish material was squeezed into the airway through a tiny opening. The locations, sizes, and appearances of the fistulas can vary as illustrated in Figs. 41.1, 41.2, 41.3, 41.4, 41.5, 41.6, 41.7, 41.8, and 41.9. Figure 41.1 shows a small opening as sequelae after radiation therapy. Clinical symptoms were discrete.

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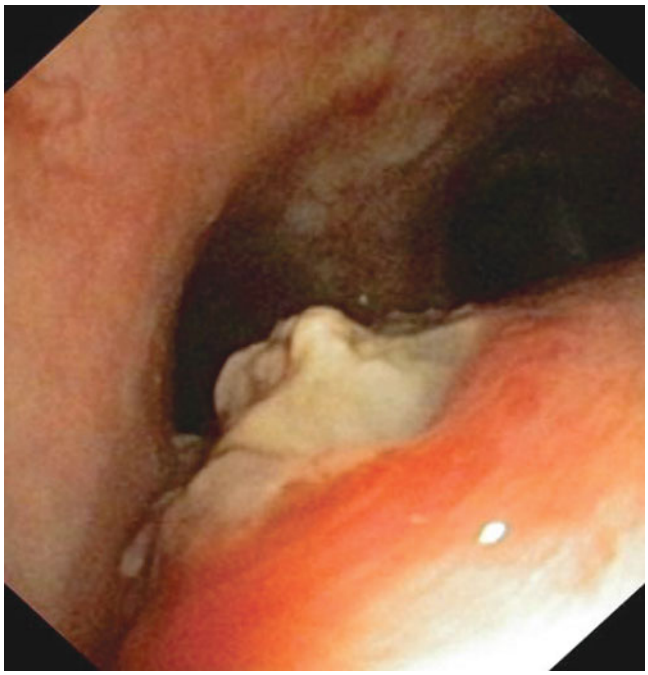


Fig. 41.1 Small fistula in the lower trachea. Whitish purulent material from the cancer occluded esophagus is seen extruding into the airways

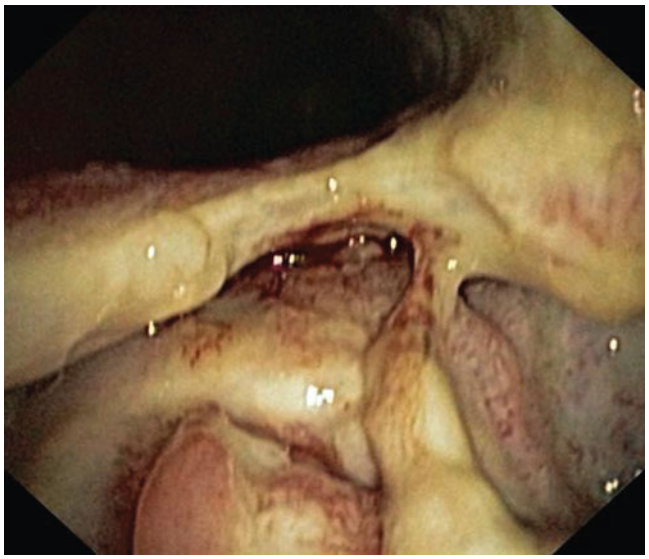


Fig. 41.3 Huge fistula after radiation therapy of a tracheal cancer. The partially necrotic esophagus can be seen through the posterior membrane of the trachea

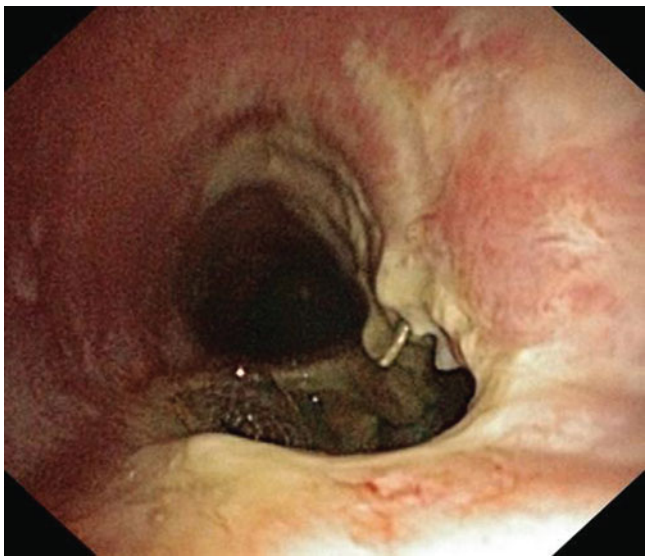


Fig. 41.2 Large fistula with necrotic edges and lymphangiosis of the tracheal mucosa

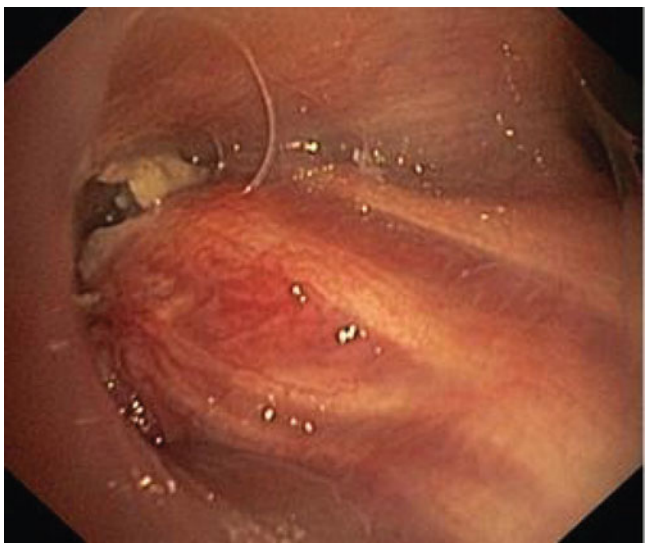


Fig. 41.4 Esophageal tumor compressing the *left* stem bronchus. The fistula opening becomes only visible if the narrowing is passed with a rigid bronchoscope

The fistula was later sealed by fibrin glue injection. Figure 41.2 is a typical example of a necrosis in tracheal cancer. The airway lumen is not compromised, but there is soilage into the lungs, promoting pneumonia.

In Fig. 41.3, the already partially necrotic esophagus starts to protrude into the lumen of the trachea. As long as no prosthesis is placed into the esophagus, breathing is not impaired. However, the necrotic edges of the tracheal fistula indicate that there will be rapid deterioration, and immediate palliation is required. Figures 41.4 and 41.5 illustrate the effect of a growing esophageal cancer on the airways. A stem bronchus or the whole carinal region can be compressed. The symptoms are intractable cough, stridor, and dyspnea.

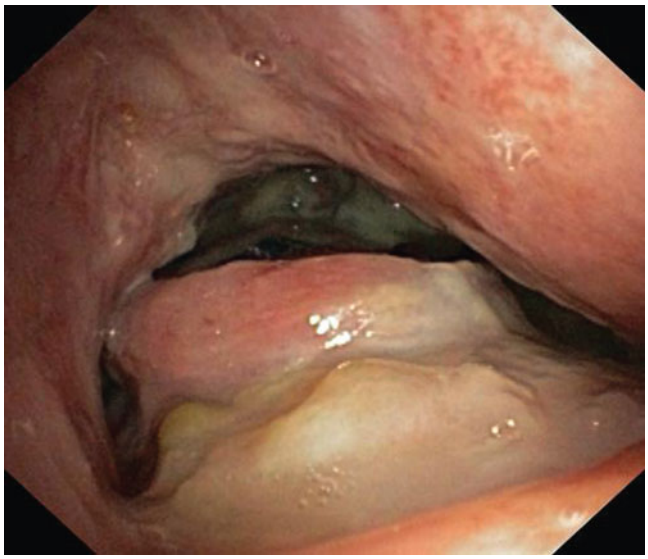


Fig. 41.5 Esophageal cancer, invading through the tracheal wall. Three communications have developed into the respiratory tract. Patient who had been dysphagic for weeks became almost asphyctic

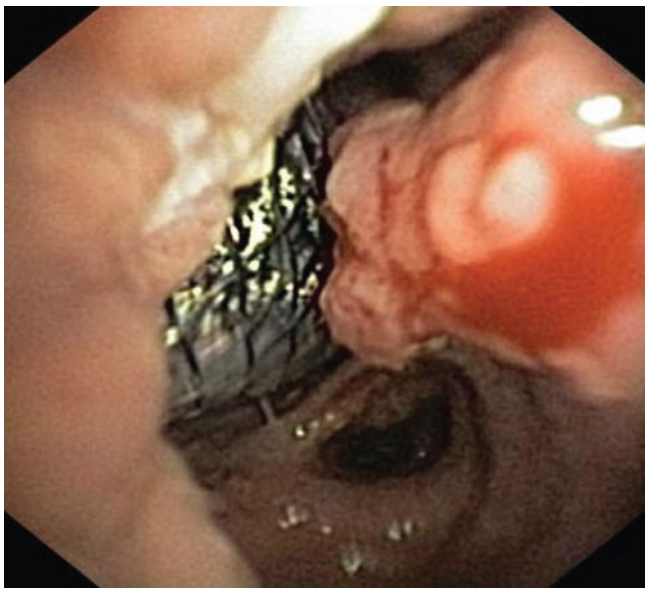


Fig. 41.7 Esophagoscopic view on an esophageal tumor (*right*) and a covered tracheal stent that had been placed in order to prevent aspiration

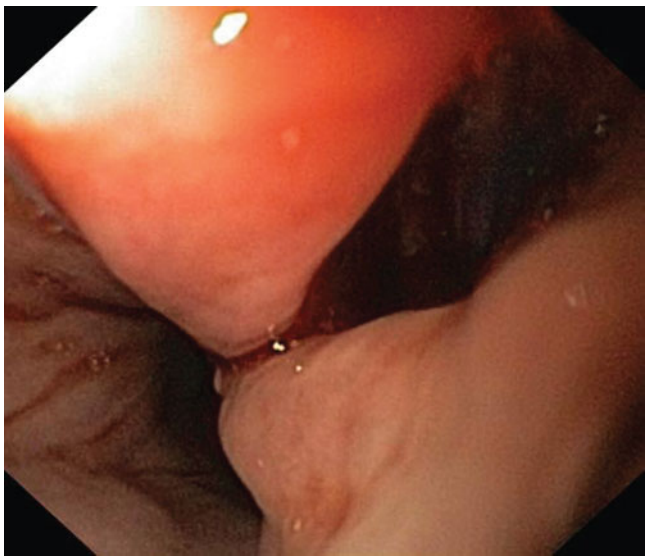


Fig. 41.6 Esophagoscopic view of a "clean" fistula following resection and radiation therapy of an esophageal cancer

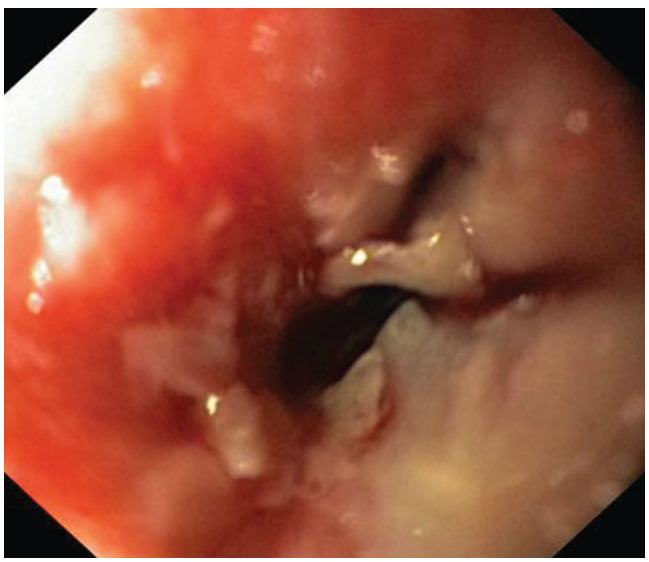


Fig. 41.8 Malignant tumor, obstructing the esophagus. The fistula is located behind the tumor and can only be seen from the bronchial side

Figure 41.6 shows a fistula with clean edges, indicating that there is no cancer, while Fig. 41.7 was made in a patient with growing esophageal cancer and a 2-cm-long fistula. A self-expanding metal stent that had been deployed into the trachea is seen from the esophagus. In all these cases, saliva and food spill over into the airways when the patient swallows, and acidic gastric content gets into the lungs.

Figures 41.8 and 41.9 show cases where only fluid either from the oral side or from the stomach gets into the respiratory tract. The cancer-affected esophagus is completely obstructed. The clinical symptoms depend on whether the fistula has developed proximally or distally of the occlusion. In any case, nutrition via the normal route has become impossible, and aspiration pneumonitis has to be expected.

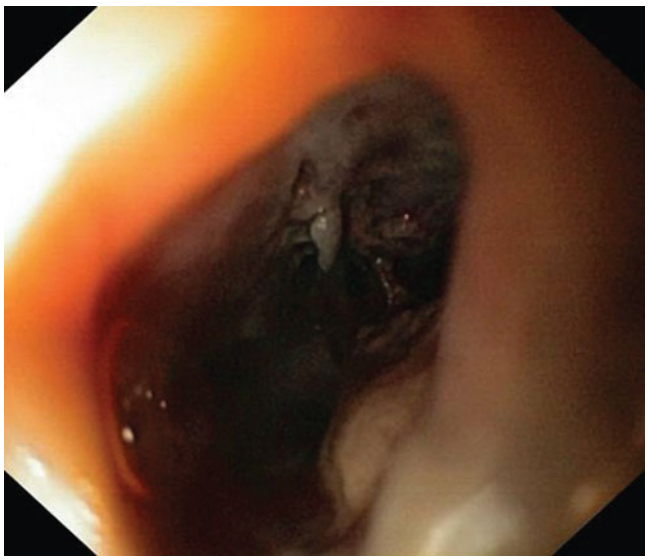


Fig. 41.9 Completely malignant destruction of the esophagus. Fistula into the stem bronchus is located distally to the necrotic cavity in the mediastinum

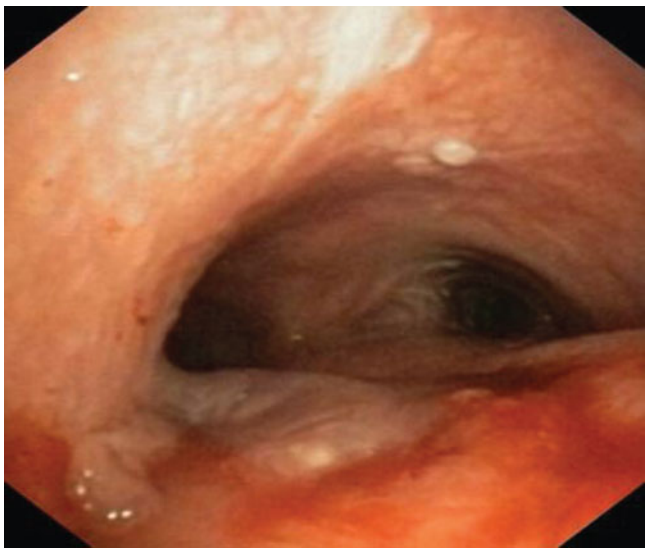


Fig. 41.10 Small fistula (sequela from radiation therapy) has been sealed with autologous fibrin

Treatment

When the diagnosis has been made, the immediate goal is preventing soilage into the lung. Patency of the airways has to be preserved or restored; swallowing of at least saliva, preferably with fluid and food, should be enabled. The therapeutic approach depends on the clinical condition, the type, size, and location of the fistula.

Benign Fistulas

Benign fistulas should be operated if the clinical condition permits. The patient should not be septic and should not require ventilator support. The surgical access with Kocher's incision, sternotomy, or posterolateral incision depends on the height of the fistula. After preparation, the fistula is dissected from the esophageal side first, followed by sleeve resection of the trachea. A muscle flap (e.g., from the m. sternohyoideus) is often used to protect the anastomoses. There are two accepted exceptions from this approach. If a fistula is very small, an attempt can be made to glue the fistula with fibrin. We have been successful in a two cases using the Vivostat® system with autologous fibrin as illustrated in Fig. 41.10.

At the other end of the spectrum are patients who are too sick for immediate surgery. Poly-trauma patients or those with complete ruptures of trachea and or esophagus should not be primarily operated. The first priority is to stabilize the clinical situation. Tube and stent placements can be used as bridging methods.

The worst scenarios are encountered if a patient with respiratory failure requires positive pressure ventilation and the walls of trachea and esophagus are eroded, e.g., by a tube cuff. The ventilator pumps air into the abdomen, further deteriorating the respiratory condition by lowering residual lung volume promoting gastric reflux into the lungs. The standard approach is by placing the cuffed tube further down into the trachea. Sometimes a double lumen tube has to be placed into a stem bronchus in order to maintain gas exchange. The drawback is that bronchial toilette with suctioning through such a tube is heavily impaired because of the small lumina. Another emergency approach that has been recommended is blocking the fistula from the esophageal side with a Sengstaken-Blakemore tube. I have personally used a dilatation balloon for that purpose. The third alternative would be the use of extracorporeal lung support devices. After the patient has been stabilized, stents can be placed.

Malignant Fistulas

Malignant fistulas can result from direct erosion of cancer into the anatomical structures or as a result of treatment. Quite often, we see patients with esophageal cancer who have received postoperative chemoradiotherapy, suddenly presenting with symptoms of fistula. This could be due to cancer recurrence, progression of disease, or late sequelae of treatment with local dehiscence. There are additive side effects of mediastinal radiotherapy if bevacizumab is administered as part of the treatment. Once a fistula has developed

in a cancer patient, his overall clinical condition declines rapidly. Most of these patients suffer already from general weakness, cachexia, dyspnea, and pain. The continuous aspiration and coughing is exhausting and creates a constant fear of eating and drinking with the consequences of further loss of weight. Inadequate clearance of purulent secretions and aspiration pneumonitis result in respiratory failure even if the tracheal lumen is not compromised. With supportive care without palliative measures, patients have a mean survival expectancy between 1 and 6 weeks. Placement of stents is considered the treatment of choice for patients suffering from these malignant fistulas.

Stent Placement

State-of-the-art stents are self-expanding structures that can be placed endoscopically. In the above-mentioned situations, we have the choice of placing such prosthesis into either the esophagus, the trachea, or into both organs (double stenting). Before discussing the techniques, I would like to elaborate on some biomechanical aspects first. Regardless of where they are placed, stents can fulfill two purposes. They can establish patency of a lumen, and they can seal a hole. Though this seems simple and obvious, there is an imminent problem. In order to open a compressed or strictured lumen, a stent has to expand inside this tubular structure by applying a certain pressure (hoop stress). Once deployed, stents are held in place by friction due to contact pressure. Mild oversizing prevents stent migration. However, if a lumen is stretched, the hole in this lumen is also stretched, resulting in enlargement of the fistula. In other words, whether a stent is placed into the esophagus or into the trachea, chances that a fistula will heal are minimized as its edges are torn apart. Therefore, stent therapy is a palliative measure that can save a patient's life and hopefully improve his quality of life, but we cannot expect it to promote healing of a fistula.

If the decision has been made to place a stent, the next questions have to answer whether single or double stenting should be performed, in which order, and by whom. The later question should not influence decision making. However, real-life conditions in most hospitals do certainly have an impact. If we get patients from outside with a single stent coming from a gastroenterologist, they have a stent in the esophagus as well as a PEG. If a patient with similar clinical problems and histories had been admitted to a pulmonologist first, they usually come with a tracheal stent and a nasogastric tube. While overall more than two thirds of fistulas result from esophageal cancers, in the prospective study from Herth, 74% of the patients had bronchogenic carcinomas, and 26% had primary esophageal tumors. Ideally, patients should have access to all methods. Fortunately, we do all procedures in our department with full support from thoracic surgeons and critical care colleagues.

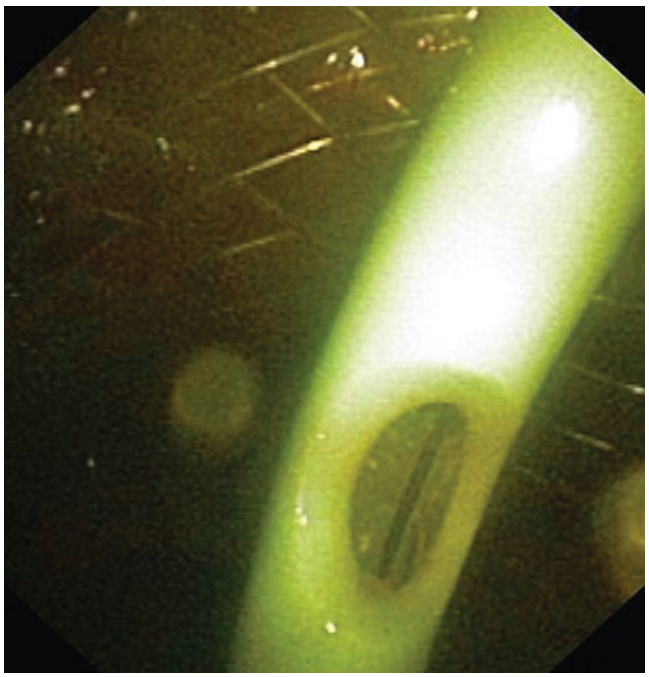


Fig. 41.11 A covered self-expanding esophageal stent is placed under direct endoscopic vision. If the stenosis is too tight, the stent can be deployed under fluoroscopical control

Placing an esophageal stent has certain advantages. Esophageal stents are round shaped like the target organ. In contrast to airway stents, these prostheses can be deployed without the risk of suffocation as the devices do not open and expand immediately. The dimensions are usually bigger. In former times, we had to insert rigid Celestine tubes, sometimes with huge cuffs which required very deep sedation or general anesthesia. At present, for most cases, self-expanding metal stents are used. They are available from several companies, in different lengths and diameters. They are inserted over a guide wire as illustrated in Fig. 41.11.

Alternatively, self-expanding polymer stents (Fig. 41.12) can be used.

Modern stents do not show much retraction which facilitates proper placement. Though it is usually feasible to deploy the stent under direct endoscopical vision, the procedure is even easier and safer with fluoroscopy if a C-bow is available. The fistula is marked with radiopaque skin markers (paper clips). The stent must be positioned so that the fistula is completely covered, ideally with a covered safety zone of 2 cm on both ends. Stents in the upper third of the esophagus cause inconvenience, and the esophageal sphincter should be respected. When treating strictures and fistulas in the lower esophagus, it might be necessary to use a prosthesis with an anti-reflux valve.

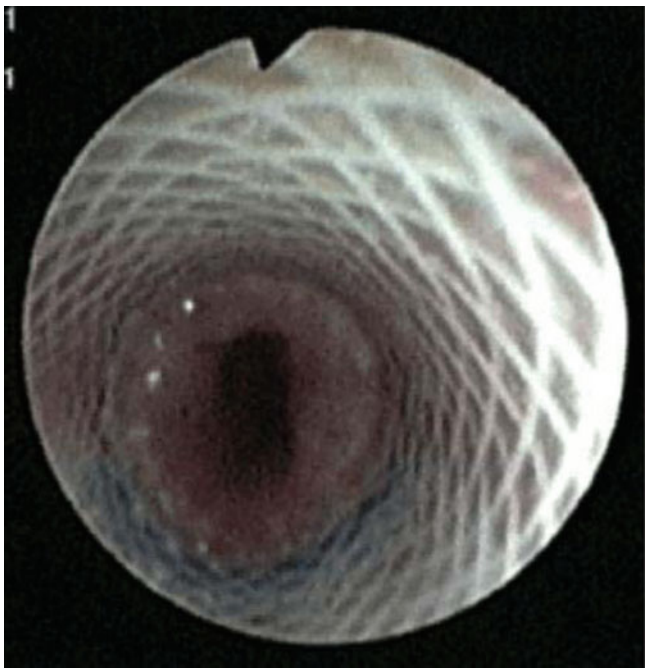


Fig. 41.12 The self-expanding Polyflex esophageal stent is an alternative to covered metallic stents

The situation is more complicated if there is a stricture or severe tumor invasion. Laser or APC can be applied through the gastroscope in order to remove endoluminally growing cancer tissue. Strictures that cannot be passed with a regular 11-mm endoscope are dilated with high-pressure balloons prior to stent placement. We usually fill these balloons with diluted contrast medium and inflate the balloons under fluoroscopy. My personal preference is to do this under general anesthesia while I have a bronchoscope in the trachea. Caution is required not to overextend the stricture and create a rupture and increase the size of the already existing fistula.

We have seen several patients with extreme strictures or tumor compressions that could not be passed with a gastroscope. With blind advancing of a guide wire, there is a risk of penetration through the fistula into the mediastinum. We use a rigid esophagoscope and insert it until the beginning of the narrowing. Next, we use a 4-mm OD bronchoscope with an air-insufflation balloon attached to the suction channel. With this modified instrument, it is usually possible to pass the narrowing and introduce a thin guide wire. Over this guide wire, we advance a gastric tube into the stomach without the risk of creating a false way (Fig. 41.13). Over this gastric tube, a stiff guide wire can be passed which finally enables to bring Savary-Gilliard dilators through the stenoses (Fig. 41.14). With increasing diameters of the bougies, the stenoses can be dilated until there is sufficient lumen for an esophageal stent. Following this multistep dilatation, a regular gastroscope can be introduced and a PEG can be placed.

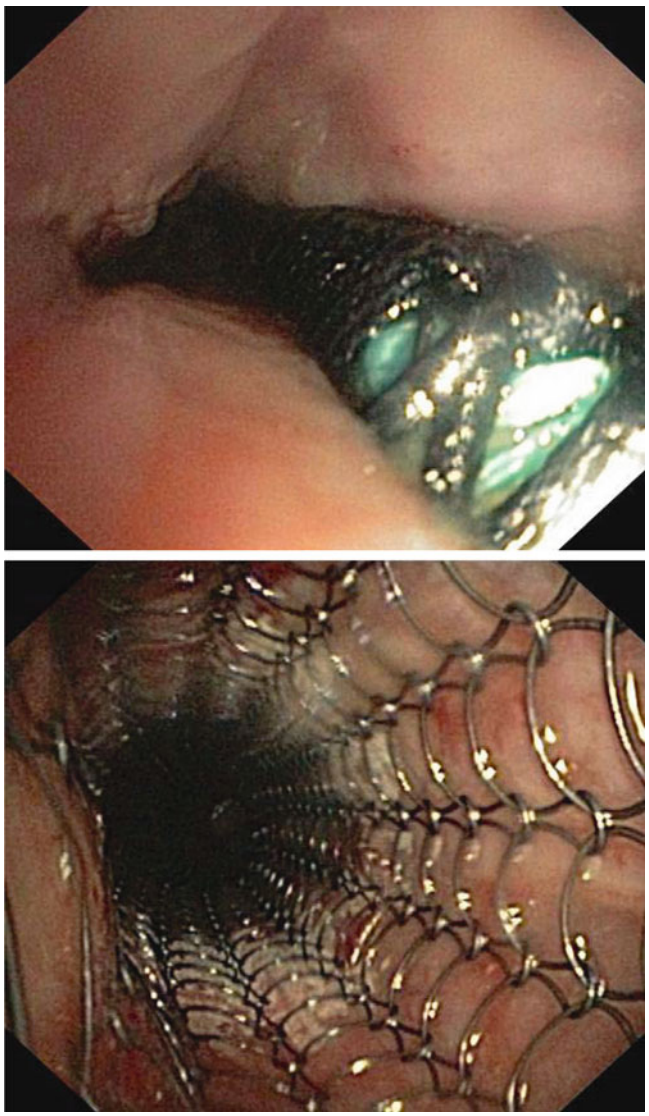


Fig. 41.13 Gastric tube, advanced over a wire, is advanced through an esophageal stent and through the almost complete obstruction caused by cancer progress. Over this wire, larger dilatation instruments can be passed into the stomach before another stent is placed

In most cases, patients can swallow their saliva which is already a great improvement in their quality of life. Alimentation is usually enabled but whether aspiration with coughing can be completely prevented depends on the size of the fistula. The literature shows that sealing with single esophageal stenting is accomplished in more than 80% of the cases.

The complication rate does not only depend on the skills of the endoscopist. With an underlying uncurable disease, progression has to be expected. Perforations in the upper esophagus are seen in about 10% of cases; migrations occur if the patient receives tumor-reductive therapy such as radiation. The complication that we see most often is cancer

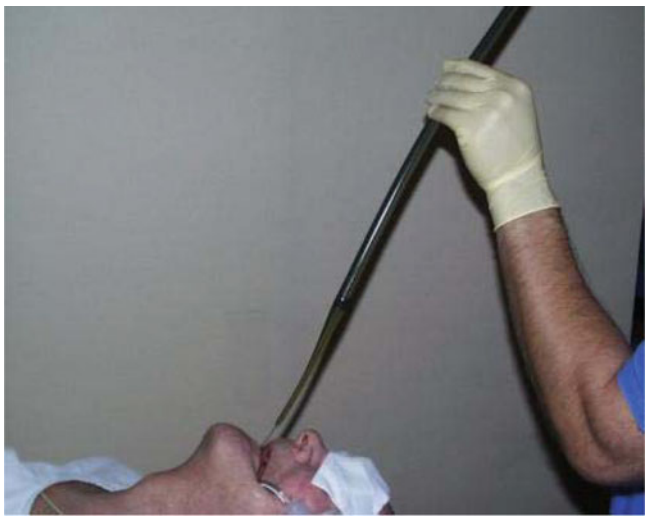


Fig. 41.14 A Savary-Gilliard bougie is used to dilate the strictured esophagus before a stent is placed. Caution is required to prevent further increase of the fistula

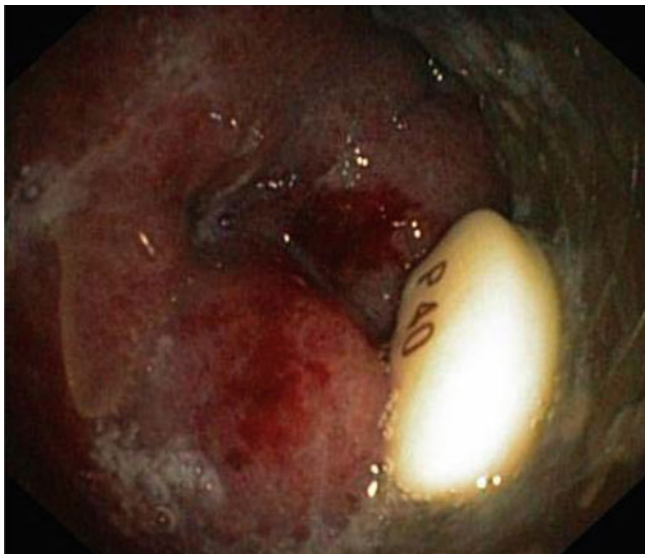


Fig. 41.15 Cancer progression distal to a self-expanding stent has caused complete obstruction preventing even the uptake of medication. Despite this obstruction, gastric content spills over into the lungs through a fistula behind the stenosis

progression with occlusion at the lower end of the stent (Fig. 41.15).

After a relatively symptom-free period, patients encounter dysphagia again, often accompanied by new aspiration symptoms. In those cases, a second or even third stent needs to be placed to enable food uptake and prevent coughing (Fig. 41.16).

Another complication is the increase of the fistula without growth of tumor mass. Swallowing is still possible but it is again followed by coughing and crackles. Figure 41.17 shows the problems from the airway side. Either the covering of the

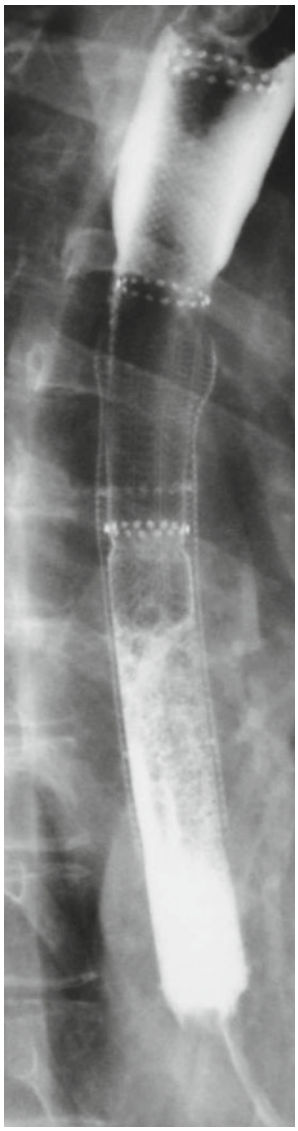


Fig. 41.16 A total of three esophageal stents was required to enable food uptake and seal a fistula

stent is too short in the first place, cancer progression has resulted in a bigger fistula (Fig. 41.17a), or the stent covering has developed a defect (17 b).Orally taken fluid or gastric content can pass through the wire meshes into the lung.

Further deteriorations are illustrated in Figs. 41.18 and 41.19. The esophageal stent has perforated through the wall defect into the lumen of the airway. Trachea or bifurcation is almost completely blocked. These are life-threatening conditions for patients. In Fig. 41.19, a silicone airway stent had been placed in order to counteract the perforating esophageal stent. It is not completely open; the expansion force of the esophageal prosthesis is too high. The respiratory tract is severely affected. There is continuous soilage into the lung. This is a clear indication for explanting both stents and replacing them with longer ones.

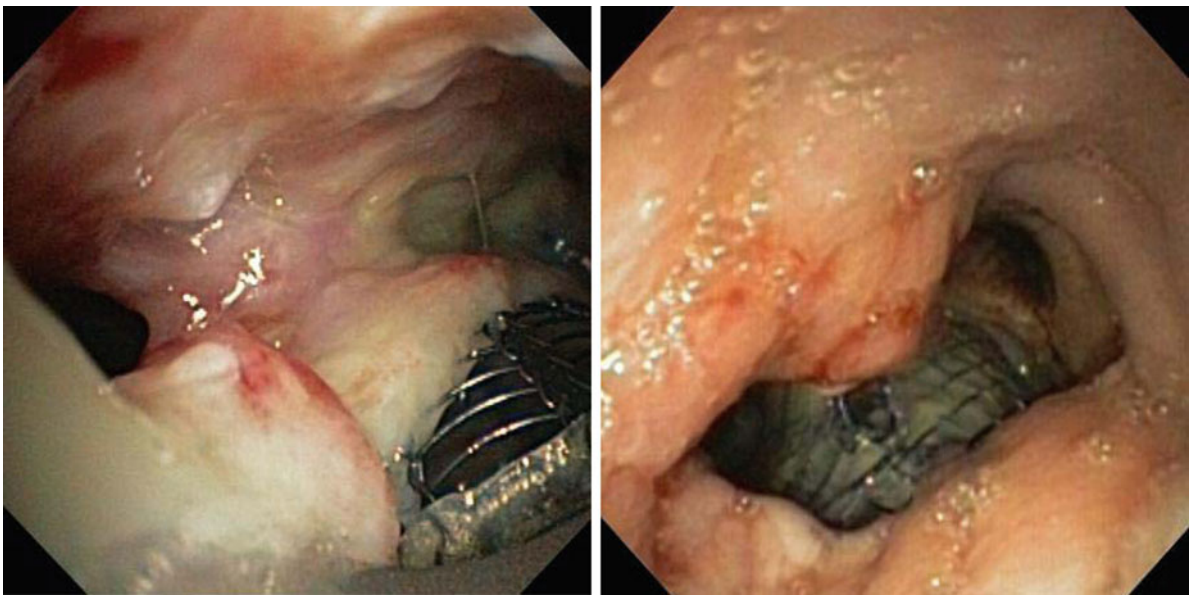


Fig. 41.17 Self-expanding esophageal stents with insufficient coverings as seen from the airway side

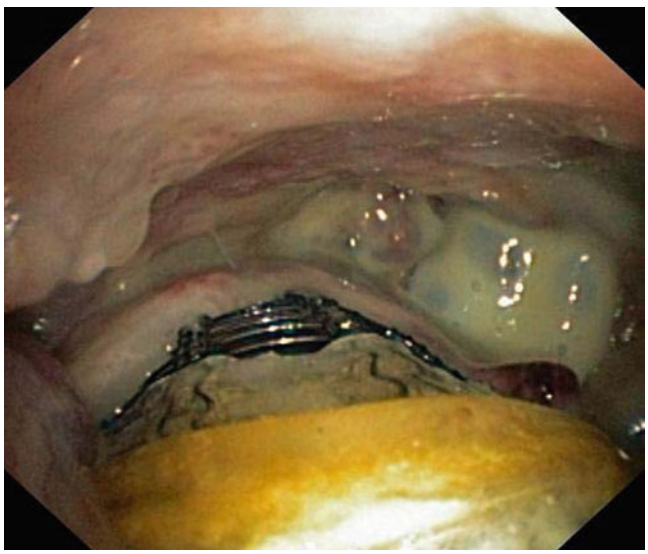


Fig. 41.18 A self-expanding esophageal stent protrudes through the posterior wall of the lower trachea and causes life-threatening obstruction

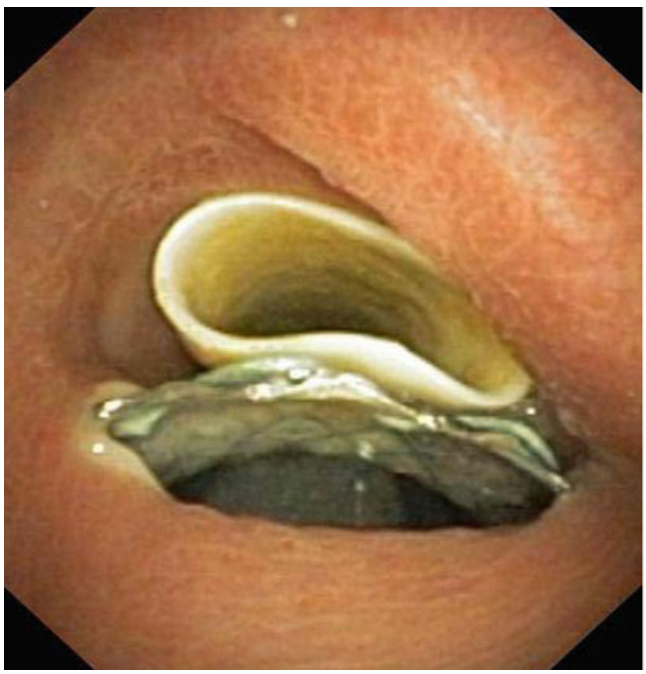


Fig. 41.19 A bifurcated Dumon airway stent had been placed to counteract the obstruction of the trachea from a self-expanding esophageal stent. Both stents had to be removed and replaced by longer ones

Airway stents are placed for several reasons. Main indications are dealing with extrinsic tumor compressions or wall destructions. If instead of a tumor mass an esophageal prosthesis squeezes a central airway, it is a reasonable indication for airway stenting. The airway stent can counteract the compression and support the sealing effect. Depending on the location and extent of the fistula, it can be managed with an airway stent alone. In 10–20% of cases, double stenting is performed (Fig. 41.20).

Airway stenting in patients with big fistulas can be a challenge. If the procedure is performed under general anesthesia, the patient needs to be ventilated adequately. Bronchoscopic jet ventilation or positive pressure ventilation is difficult because the air is pressed into the mediastinum or abdomen. As mentioned before, one way to manage this

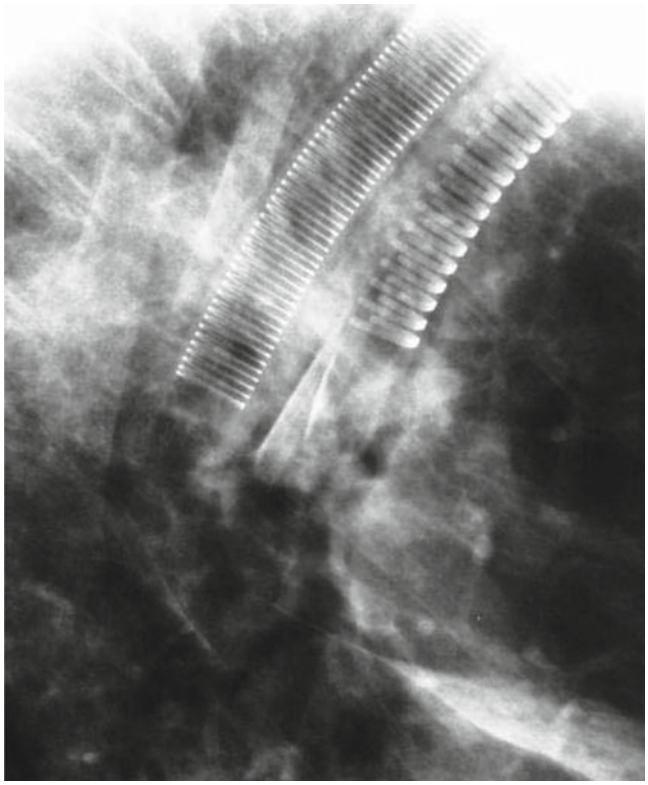


Fig. 41.20 Double stenting of esophagus and trachea. Lateral view on a chest X-ray

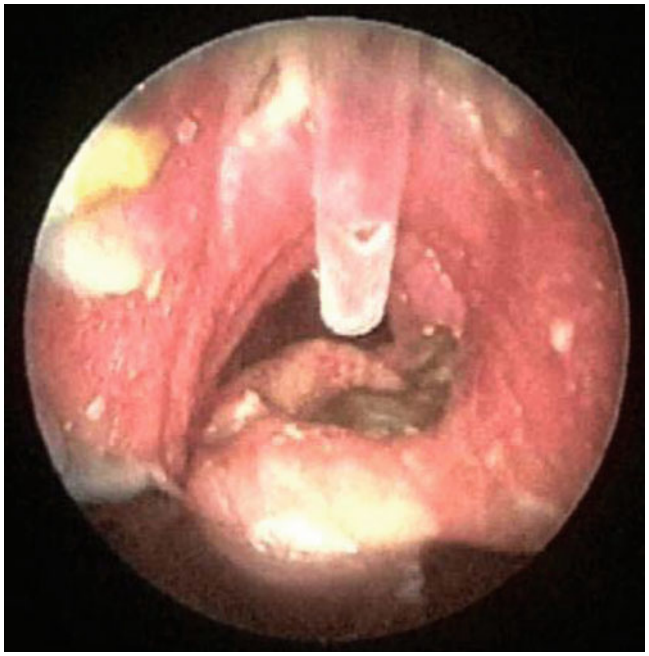


Fig. 41.21 A jet catheter is used to ventilate the patient during the endoscopic procedure

situation is using a temporarily sealing balloon in the esophagus or placing an esophageal stent before the respiratory tract is approached. If the defects are large, there is the risk that the esophageal devices protrude into the trachea and impair ventilation. We prefer to place a rigid bronchoscope first: either pass it over the fistula to the carina or even into a stem bronchus and then work on the esophagus. Occasionally, we have used a jet catheter placed behind the fistula opening (Fig. 41.21) in order to ventilate the patient during the procedure.

Another option is to place a small endotracheal tube next to the bronchoscope and the esophagoscope (Fig. 41.22). This secures the airways and enables gas exchange while providing endoscopic vision on the fistula from the esophageal as well as the tracheal side.

There are several methods to confirm proper positioning of the devices and sealing efficacy. Figure 41.23 shows transillumination using a 90° telescopic lens in the esophageal stent and looking into the trachea with a bronchoscope. The defect is seen, and contact between the two prostheses and sufficient sealing is confirmed.

Another option is the methylene blue test (Fig. 41.24). Blue ink is injected into the esophagus. Bronchoscopy shows that no ink enters the airway through the covering of the

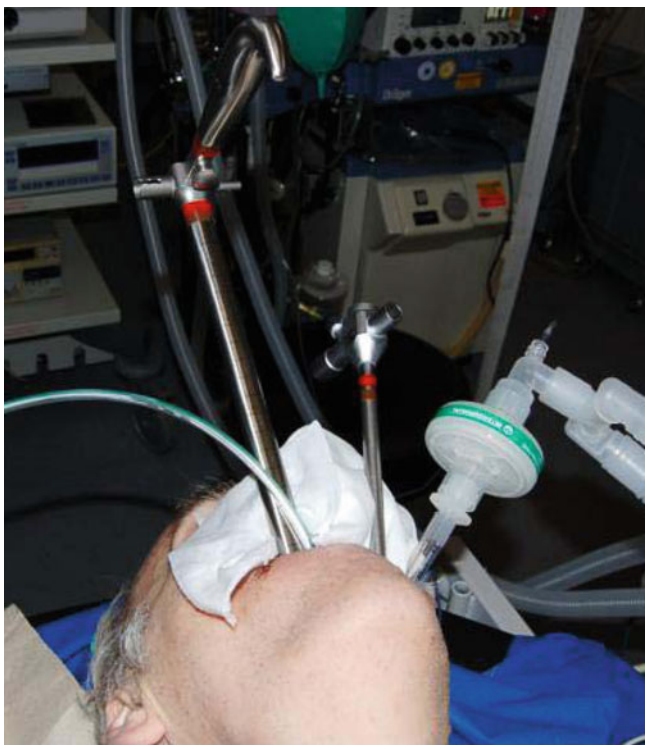


Fig. 41.22 Multi-intubation. A small endotracheal tube with a cuff distally to the fistula is used to ventilate the patient, while tumor masses are reduced and strictures are dilated through the rigid bronchoscope and the rigid esophagoscope. A gastric tube is used to pass a wire into the stomach before stent placement

esophageal stent. It is advisable to ask the patient to swallow and cough during the procedure. Subsequently, they need to perform the Müller and Valsalva maneuver. If there is no spill over of blue fluid during these maneuvers, then patients may be permitted to drink and eat regular food without risk of aspiration.

Finally, a gastrografin swallow can be used (Fig. 41.25) to demonstrate the success or failure of the interventional procedure.

In small series, there were no significant differences regarding the clinical benefits or survival times when patients received airway stents, esophageal stents, or both. Resolution of pneumonias, restoring airway patency, and food uptake could be accomplished with any method. Success rates have been reported between 76% and 86%. However, there has been no controlled study. In all series (retrospective and prospective), doctors opted for the method they considered most appropriate for an individual patient. Mean survival times after stenting range between 25 and 250 days if the fistula can be sealed. Newer studies with self-expanding covered metal stents instead of semirigid esophageal prostheses yielded better results. Patients with double stenting lived on average 50 days longer than patients with one stent only, but there has always been a severe selection bias. Longer survival was seen if antineoplastic therapy was added with no differences between radio- and chemotherapy. Regarding fistula location, patients with fistulas in the right stem bronchus had the worst clinical outcome. If a patient with an esophago-respiratory fistula is ventilator dependent or septic, his prognosis is very poor. We have only been successful in getting a few patients off the respirator if they were intubated and had a malignant fistula.

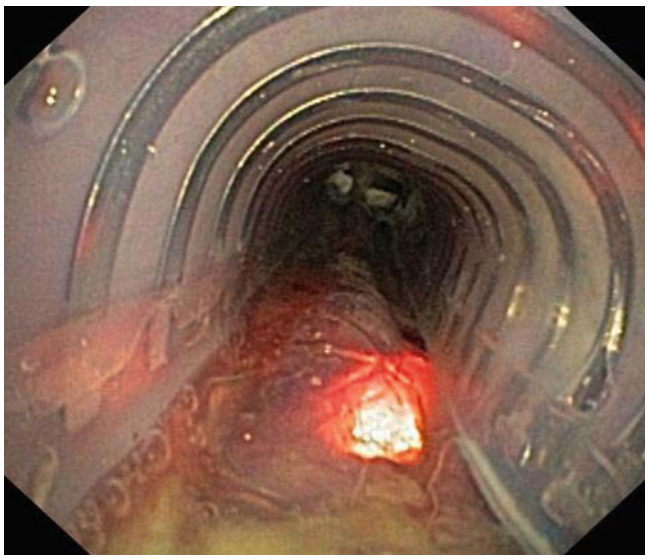


Fig. 41.23 Bronchoscopic view into an anatomically shaped dynamic stent. Diaphanoscopy through a rigid esophagoscope is used to confirm proper position and sealing of the esophageal stent

It has already been mentioned that stent insertion intended to seal a fistula stretches it by applying expansion force in the tubular structures. There is another basic mechanical problem if we try to seal larger esophago-respiratory fistulas. Most protheses are round shaped. The contact area which is the sealing area is small in relation to the circumference of the devices (Fig. 41.25). Stents with expansion forces strong enough to open stenoses cannot adapt to irregular shapes. This becomes especially relevant in patients with partial resection of the esophagus and pulling up of the stomach. Standard devices cannot fill the gap as illustrated in Fig. 41.26. For this reason, we prefer to

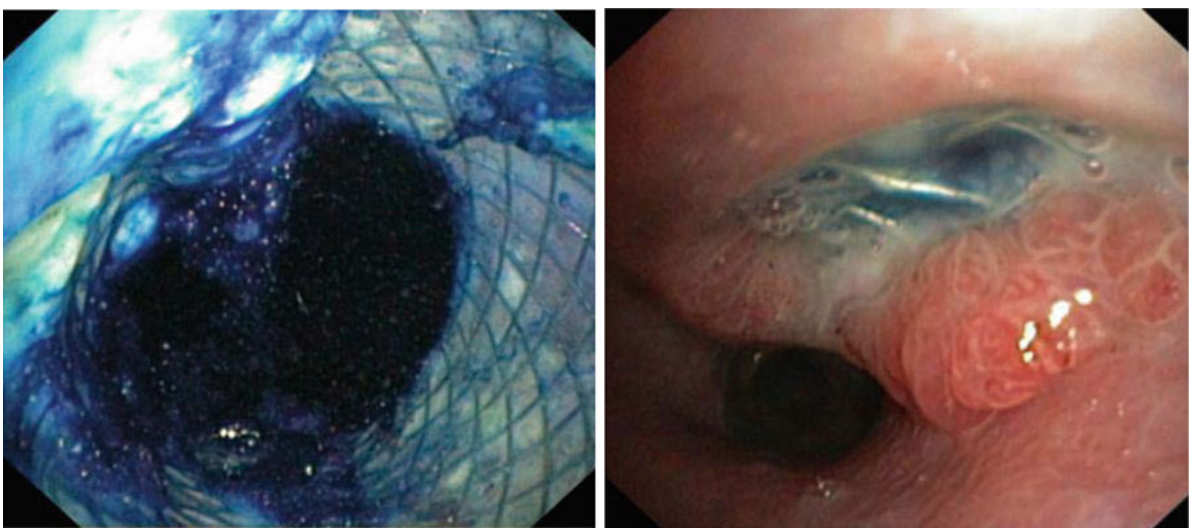


Fig. 41.24 Methylene blue test used to confirm proper sealing of the fistula. The *upper* panel demonstrates the injection of methylene into the esophageal stent, and the *lower* panel confirms that no ink enters the airway on bronchoscopy

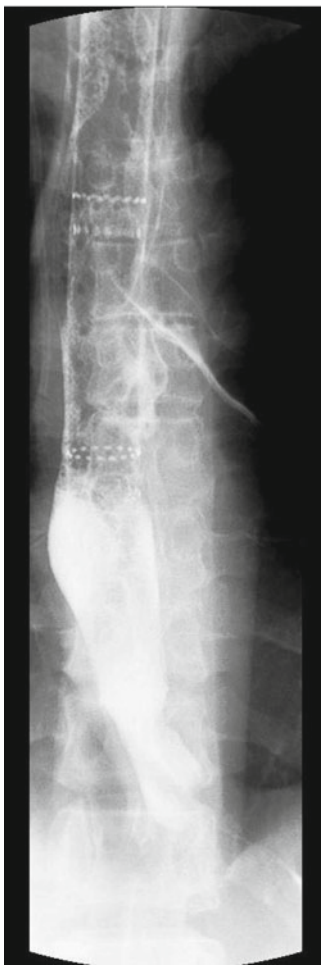


Fig. 41.25 Gastrografin swallow reveals incomplete sealing by outlining the *left* stem bronchus

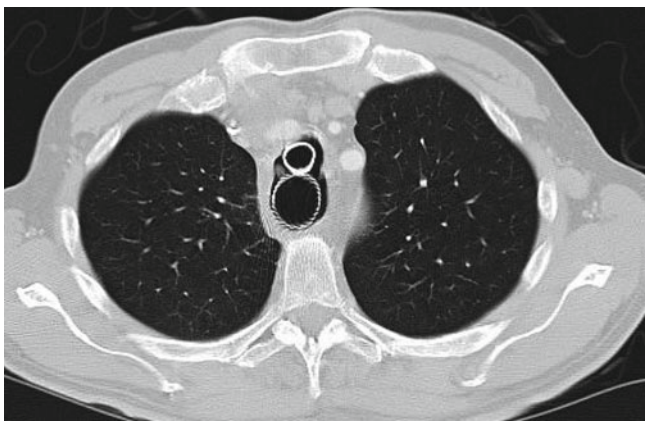


Fig. 41.26 CT shows the relatively small contact zone between the two prostheses

insert a Dynamic stent which has a concave-shaped posterior wall into the trachea in combination with a self-expanding covered metal stent or a flexible esophageal Polyflex stent in the esophagus (Fig. 41.27). With this combination, we have got the best clinical results though this has never been proven in a study.

For most patients, it is already a major improvement in their quality of life if they can swallow without the excruciating coughing attacks. Prevention of aspiration pneumonia is most important for the prognosis, but ideally, we want to accomplish sufficient alimentation. Unfortunately, all sealing techniques have limitations, and most patients do not eat enough despite stent placements. For this reason, it has become our standard of practice to insert a PEG at the end of the above-mentioned procedures. Most patients give their consent to this measure especially as we do it in the same session that we place the stents under general anesthesia. Depending on the outcome, we administer more or less nutrition through the PEG (Fig. 41.28).

Figure 41.29 summarizes my personal recommendations, based on literature review and personal experience. Benign fistulas should be operated. For small fistulas, an attempt with autologous fibrin sealant is justified. Malignant fistulas with esophageal stenoses should be treated with dilatation and esophageal stents. A completely occluded esophagus should be opened with endoscopic techniques; if this is impossible, surgical bypass techniques must be considered. Central airway obstructions require an airway stent, often double stenting is the most promising approach. PEGs should be provided generously because they can provide nutrition without complete dependence on the sealing efficacy of the above-mentioned procedures.

Newer Techniques

There are no dedicated sealing devices for esophago-respiratory fistulas. Double stenting combined with radiotherapy is probably the most efficient technique for the palliation of malignant fistulas. Recently, there have been case reports about the successful use of atrial septal occluders. The normal Amplatz devices are certainly not ideal for the tubular structures that we are dealing with here. Esophago-tracheal fistulas will remain a clinical problem for the years to come. Interventional endoscopists will have to deal with them, and we can only hope that the industry provides us with better suited devices in the near future.

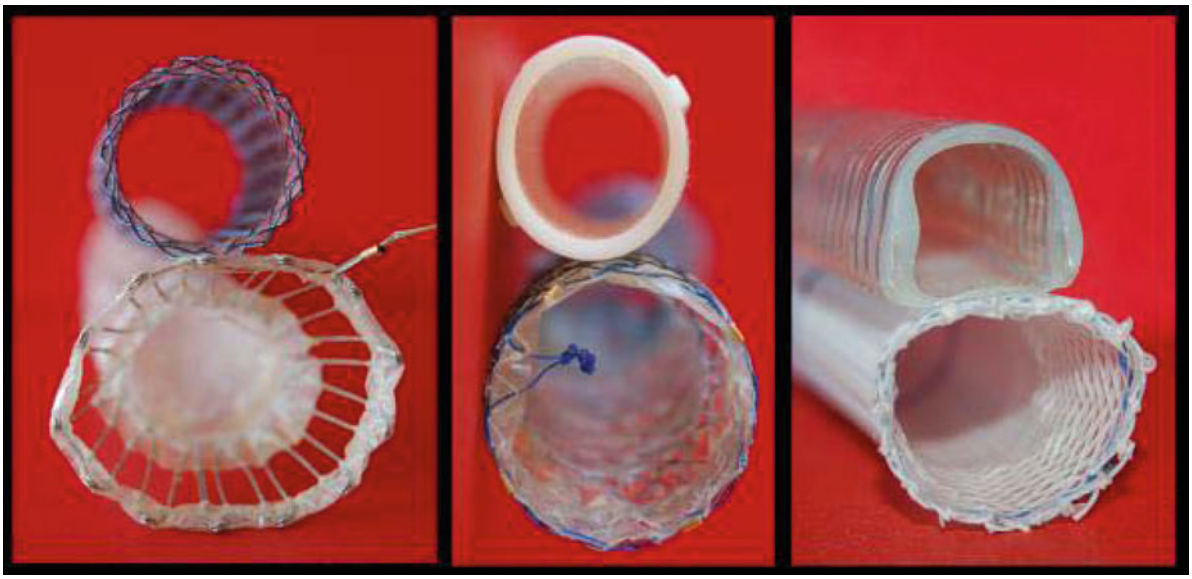


Fig. 41.27 Various combinations for double stenting. A concavely shaped tracheal stent combined with a convexly shaped esophageal stent yields the best sealing

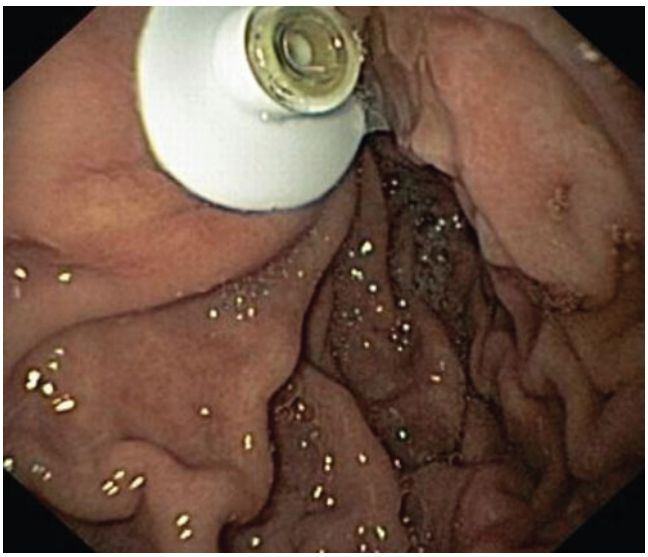


Fig. 41.28 A PEG is placed at the end of the procedure

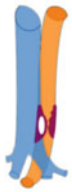
Illustration	Clinical Condition	Treatment Esophagus	Airway	PEG
	radiogenic stricture small communication coughing, pneumonia, dysphagia	esophageal stent (fibrin glue)	fibrin glue	(+)
	Inflammatory no narrowing spill over from saliva and gastric content	surgery whenever possible (stent) (atrial septal occluder)	surgery with muscle flap	+
	malignant stenosis of esophagus dysphagia, aspiration of saliva and gastric fluid	esophageal stent anti-neoplastic treatment	(airway stent)	++
	malignant obstruction of esophagus aspiration of gastric fluid into airways	laser, APC if possible saliva fistula	airway stent	If possible PEG otherwise gastrostomy
	tracheal tumor fistula into esophagus aspiration and dyspnea	(esophageal stent)	laser, APC airway stent	(+)
	tumor obstructing trachea and esophagus dyspnea, dysphagia, aspiration	esophageal stent	airway stent	+++

Fig. 41.29 Treatment recommendations by clinical condition

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Endoscopic Management of Bronchopleural Fistulas

42

David M. Berkowitz

Introduction

A bronchopleural fistula (BPF) is an abnormal communication between the airway (bronchial tree) and pleural space. It is most commonly seen after thoracic surgery; however, it can occur in many other benign and malignant diseases. Bronchopleural fistulas can be classified as either central (visibly seen as a hole in the large airways, such as a stump leak after surgery) or peripheral (non-visible if airleak is located in distal airways or on the visceral pleural surface). Diagnosis is challenging and often delayed. As a BPF represents a communication from the non-sterile airway to the sterile pleural space, it is critical to identify a fistula and initiate treatment in a timely fashion. Although surgical techniques have improved, mortality remains high even with successful operative intervention. Advances in therapeutic endoscopic techniques have provided an adjunct to traditional surgical procedures.

Nonsurgical Etiologies of BPF

A bronchopleural fistula can form in any situation where tissue necrosis and/or impaired mucosal healing after trauma or infection can occur. Necrotizing lung infections (bacterial, tubercular, fungal pneumonia, or abscess) or empyema can lead to BPF. The pooling of secretions and loss of tissue planes due to necrosis creates a poor healing environment and possible development of a fistula tract. Penetrating trauma to the visceral pleural surface (as seen with a gunshot wound, stabbing with a knife, or iatrogenic by a thoracentesis/biopsy needle) can lead to a pneumothorax with leakage of air through the puncture site into the pleural space. If the defect is small enough and the underlying lung parenchyma is not too diseased, the pleural surface heals and the defect closes. A persistent pneumothorax (>72-h) indicates that the defect is not closing and there is a continued communication between the airway and pleura. Rupture of lung tissue, whether spontaneous or related to underlying lung disease (bullae, COPD, ARDS, pulmonary fibrosis), likewise can lead to a persistent defect in the visceral pleura and BPF formation.

Lung or airway malignancy with endobronchial involvement can lead to loss of airway integrity and fistula formation. Mediastinal malignancies such as lymphoma or thymoma can directly invade into the airway which may lead to a fistula tract into the mediastinum or pleura. A dramatic response to treatment (either by radiation or chemotherapy) of a malignancy which has a large bulk of tumor invading into the airway can be problematic if the tumor "melts" away and no normal tissue is available to fill in the defect (Fig. 42.1). Esophageal malignancy with erosion into the airway typically leads to a tracheo- or bronchoesophageal fistula; however, once the integrity of the airway wall is compromised, a communication can form between the airway and the mediastinum or pleural space. Likewise, severe gastroesophageal reflux disease complicated by Barrett's esophagus or Boerhaave's syndrome may cause enough airway inflammation to create a fistulous tract. A comprehensive list of the etiologies of a bronchopleural fistula can be found on Table 42.1.

Postoperative Bronchopleural Fistula

Surgery on the thorax, especially pulmonary resection, is the most common etiology of a bronchopleural fistula (BPF). The incidence is highly dependent on surgical technique, complexity of surgery, and experience of the surgeon. Postoperative bronchopleural fistula has been reported to occur in 1.5–28% of all pulmonary resections. Multiple surgical and nonsurgical risk factors have been associated with the development of postoperative BPF (Table 42.2). Surgical

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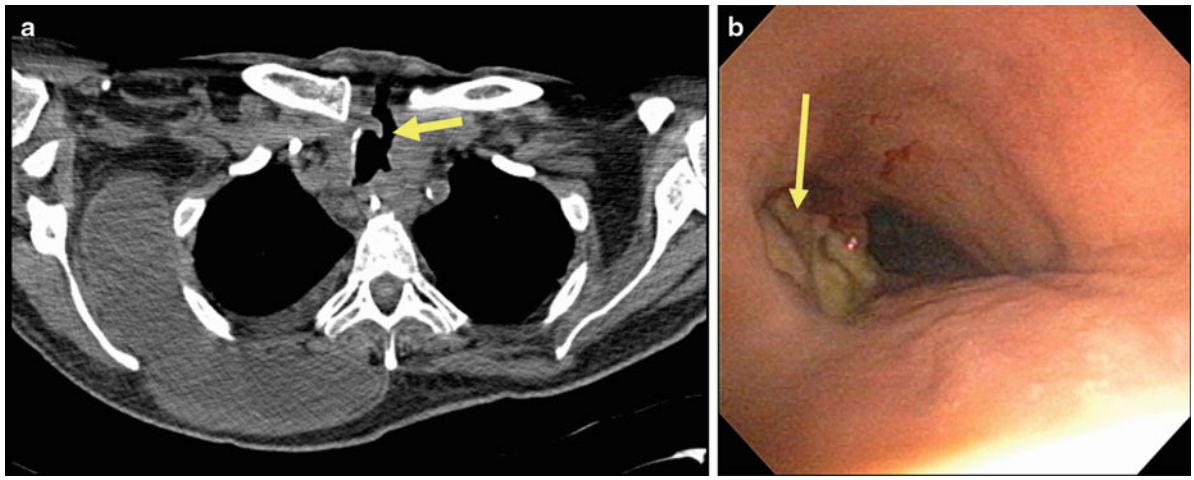

Fig. 42.1 Airway fistula developing as a result of treatment for lymphoma. (**a**) A 48-year-old man with B cell lymphoma who underwent chemotherapy and radiation. Lymphoma had eroded into the trachea, and after effective chemotherapy, large airway defect (*arrow*) was present. (**b**) Corresponding endoscopic view of tracheal wall defect

Table 42.1 Etiologies of bronchopleural fistula

Postoperatively after lung resection
Necrotizing pulmonary infection
Haemophilus influenzae
Streptococcus viridans
Staphylococcus aureus
Pseudomonas aeruginosa
Klebsiella pneumoniae
Pneumococcus
Nonhemolytic streptococcus
Aspergillus
Histoplasma capsulatum
Pulmonary abscess rupture
Malignancy (lung, thyroid, lymphoma, esophageal)
Advanced disease with tumor eroding into airway
Recurrence at stump from prior resection
Radiation therapy
Penetrating thoracic trauma
Complication of percutaneous lung needle biopsy, thoracentesis
Persistent spontaneous pneumothorax
Rupture of bullae or cyst
ARDS
Gastroesophageal reflux disease with Barrett's esophagus
Boerhaave's syndrome
Idiopathic

Table 42.2 Risk factors associated with increased risk of postoperative bronchopleural fistula

Surgical factors
Right-sided pulmonary resections (especially right pneumonectomy)
Excessive peribronchial or paratracheal dissection
Long bronchial stump/short distance from tumor to stump
Mediastinal lymph node dissection
High-dose preoperative radiation therapy
Residual/recurrent carcinoma at surgical stump
Postoperative infection (pneumonia, abscess, empyema)
Nonsurgical factors
Hypoalbuminemia
Cirrhosis
Haemophilus influenzae in sputum
Residual tumor at stump
Postoperative mechanical ventilation for >24 h

complexity and extensive dissection are important risk factors. Although postoperative BPF may be seen in up to 20% of pneumonectomies, this complication is seen in only about 0.5% of lobectomies. Right-sided surgery is an important risk factor for BPF formation. A 10-year review of surgical data demonstrated almost threefold higher risk of BPF after right pneumonectomy compared to left (13.2% vs. 5.0%, $p=0.047$). A subsequent meta-analysis demonstrated BPF to be an independent risk factor for death after right pneumonectomy with a relative risk (RR) of 3.39 for death after right pneumonectomy. Right-sided operations are technically more complicated and more likely to involve extended dissection, hand-sewn closures, closed buttress, or intrapericardial dissection. Postoperatively, right-sided stumps also tend to pool secretions more which can impair complete healing. In patients undergoing pulmonary resection for malignancy, a longer bronchial stump was an independent risk factor for BPF. Patient factors including diabetes mellitus, concurrent steroid use, hypoalbuminemia, cirrhosis, *Haemophilus influenzae* in sputum, residual tumor at stump, and postoperative mechanical vent for >24-h postsurgery have all been implicated in the development of a postoperative BPF.

Clinical Presentation

Postoperative Patient

The presentation of a bronchopleural fistula developing acutely (within hours to days) after surgery is fairly dramatic. It is heralded as the sudden onset of dyspnea, subcutaneous emphysema, cough w/ purulent sputum, or a life-threatening tension pneumothorax. Thoracic surgery patients invariably have a chest tube in the immediate postoperative period to avoid or immediately identify this complication. A continuous airleak or increase in the output of air in the waterseal chamber of a pleural fluid collection container should alert the physician to the possibility of a bronchopleural fistula. Bronchopleural fistulas identified within the first 4 days postoperative should return for re-exploration and closure of the stump leak if clinical situation allows.

The subacute (postoperative day 7–30) or chronic presentation (postoperative day >30) for a bronchopleural fistula is less impressive. Patients complain of fatigue, wasting, dyspnea, low-grade fevers, or productive cough. Hemoptysis or metalloptysis (coughing of surgical material) has been described. After pneumonectomy, there is an expected degree of and air and fluid present for at least a few weeks. The space is usually obliterated within 7 months. A major decrease in pleural effusion or dramatic change in the air–fluid pattern (increasing pneumothorax, changes in hydropneumothorax level, new air–fluid level) after pulmonary resection should raise concern for a postoperative BPF. Depending on type of surgery and loculation(s) in the pleural space, subtle changes may not be readily visualized on a plain chest radiograph. In the chronic setting, bronchopleural fistulas typically occur as a result of chronic pleural space infection or fibrosis, usually in an immunocompromised patient. Reappearance of air in a previous obliterated space is an ominous sign for BPF. Overall, bronchopleural fistulas are most commonly diagnosed between 8 and 12 days postoperative.

Non-postoperative Patient

The presentation of a BPF in the non-postoperative patient depends on the characteristics of the underlying disease. Most patients will have fever, persistent cough, thick and/or copious sputum production, and a pleural effusion with an air–fluid level. A patient with existing pneumonia or empyema, however, may already be exhibiting these symptoms leading to a delay in diagnosis. A non-resolving pneumonia, infiltrate, or effusion, especially in a patient with underlying lung disease, should warrant further investigation. In patients on mechanical ventilation, an abrupt and significant decrease in airway pressures should raise concerns for BPF formation. Hemoptysis may occur in malignancy-related fistulas, and cough and SOB during eating can be seen with esophageal to airway fistulas.

Diagnosis

Most patients with symptoms compatible with a BPF will initially be evaluated with a chest radiograph. Findings on radiographs may be nonspecific and include pneumothorax, subcutaneous emphysema, and/or pneumomediastinum. In a postoperative patient, a fluid collection adjacent to the stump may be identified. Although a computer tomography (CT) of the chest is much more sensitive at identifying abnormalities related to a BPF, it likely will not identify the location of the fistula itself. In a small study by Westcott and Volpe in 1995, in patients with clinical suspicion for BPF, the fistula site could be isolated on a CT scans in only 50% of the patients. Figure 42.2 demonstrates the radiographic appearance of a BPF.

Bronchoscopy should be performed in all patients suspected of having a BPF. In large or central lesions, it may be possible to directly visualize the fistula opening. In the case of a suspected postoperative BPF, the stump should be closely examined. If stump dehiscence is not seen, saline should be instilled onto the stump. The presence of continuous bubbling of saline from the stump indicates a fistula is present (Fig. 42.3). In the immediate postoperative patient, installation of methylene blue onto stump can be performed. Its presence in the chest tube output indicates a BPF is present.

If a fistula cannot be seen within the central airways, a bronchoscopy can still be helpful in determining the approximate location of a peripheral bronchopleural fistula. In patients with a chest tube, a balloon can be inserted via the working channel of the bronchoscope and inserted into the segment or subsegment of the airway with suspected fistula (Fig. 42.4). Once inflated, the balloon will occlude airflow

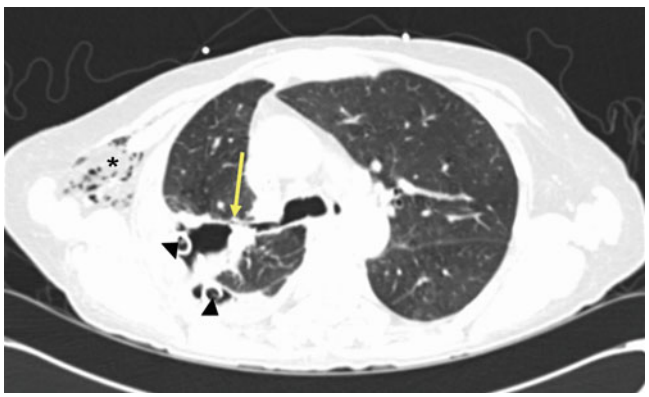

Fig. 42.2 CT appearance of BPF (*arrow*) in right upper lobe. Note chest tubes (*arrowhead*) and subcutaneous emphysema (*asterisk*) in this postoperative patient

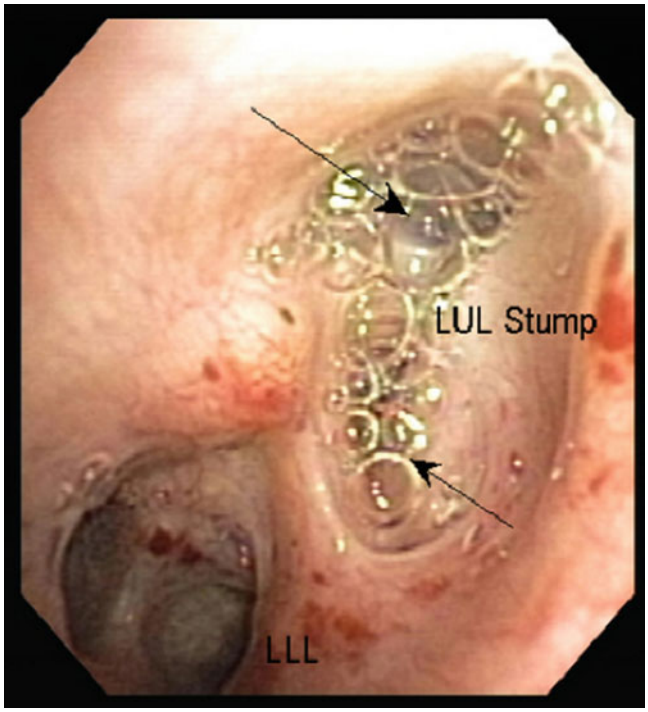

Fig. 42.3 A 70-year-old woman s/p LUL lobectomy with stump leak. Saline injected via flexible bronchoscope indicated continuous air bubbling (*arrows*) back through stump

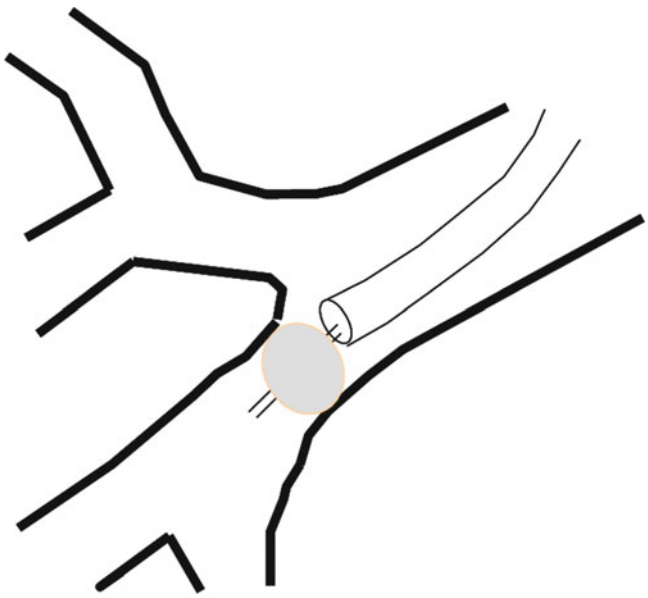

Fig. 42.4 Bronchoscopic localization of a peripheral BPF. Inflating a balloon within airway leading to a BPF will stop airflow into effected airway. This will either (1) slow or stop the airleak in waterseal chamber of pleural collection system or (2) lead to a persistent negative pressure measured by the Chartis™ system

through the fistula, and therefore, the airleak will decrease or disappear in the waterseal chamber of a pleural collection device. If the segment does not contain a fistula, inflation of the balloon will have no impact on the airleak. If even the general location of the fistula is unknown, a larger balloon can be inflated in the larger airways before proceeding to the segmental bronchi to provide the bronchoscopist with the general location of the fistula. In some cases, more than one airway may be contributing to a fistula so multiple balloon inflations may be necessary to identify the culprit airways.

A peripheral BPF can also be identified by a change in the pressure of the airway leading to the fistula. The Chartis System (Pulmonx, Redwood City, CA) is able to measure airflow and pressure in the airway distal to the bronchoscope (Fig. 42.5). It was originally designed to quantify collateral ventilation for endoscopic lung volume reduction. Once the bronchoscope is navigated to the target airway, a balloon catheter is inflated and the airway is occluded. The tip of the catheter has a pressure sensor which provides measurement of airflow and pressure in the occluded airway (Please see Fig. 42.5 for details). As long as the airway is intact and there is adequate seal with the balloon, a small or no drop in pressure will occur with balloon inflation. If the pressure remains negative during both inspiration and expiration, a BPF is present. Capnography (measurement of exhaled carbon dioxide) can also be helpful in identifying the location of a fistula. A polyurethane catheter attached to a capnometer can be placed through the bronchoscope and inserted into sequential airways. During exhalation, carbon dioxide should be detected within the airway. The absence of an end tidal CO_2 tracing in a particular segment identifies the segment with the fistula as the carbon dioxide leaks out into the pleural space. Both airway pressure measurement and capnography are useful in identifying BPFs in patients without chest tubes or in situations where subtle changes in bubbling through the waterseal chamber occur when a balloon is occluding airflow.

Advanced imaging techniques may be helpful in the diagnosis of a bronchopleural fistula. Bronchography can be done if any of the above-mentioned bronchoscopic techniques are inconclusive. In bronchography, 20–30 mL of a water-based nonionic low osmolar iodinated contrast medium (i.e., Omnipaque, GE Healthcare) is injected through a catheter placed through the working channel of a bronchoscope (Fig. 42.6). Fluoroscopy or CT can then be performed with visualization of contrast media extravasation from a site of a bronchopleural fistula. Scintigraphy with 99mTc-albumin (Technetium-albumin) colloid fog inhalation has been described as a simple and accurate test for the detection of BPF. This is accomplished by aerosolization of a radiotracer and inhalation into the lungs with accumulation of the radiotracer at location of a BPF. This technique requires substantial time and cooperation on the part of a non-intubated patient and can be inconclusive in the setting of small fistulas or underlying lung disease such as COPD. Alternatively, ventilation scintigraphy with other radioactive tracers such as 81mKr (Krypton), 133Xe (Xenon), 99mTc-DTPA

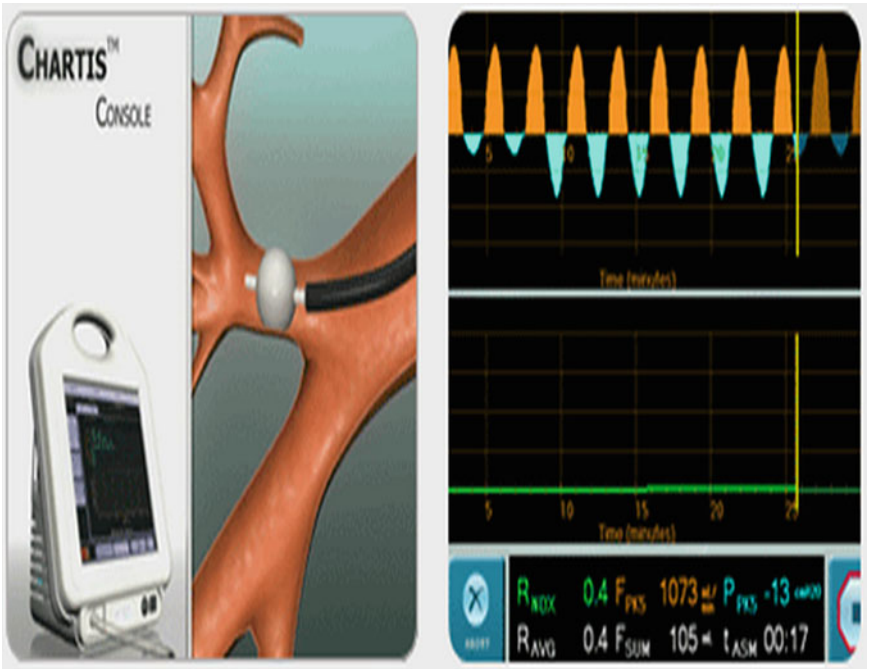

Fig. 42.5 Chartis™ system developed for endoscopic LVRS can be helpful in localizing a BPF. The balloon is inflated and a pressure sensor at the end of the balloon measures both pressure and flow distal to the occluded bronchus. A significant negative pressure during both inspiration and expiration indicates a segment involved in a BPF (© 2010 Pulmonox. All Rights Reserved)

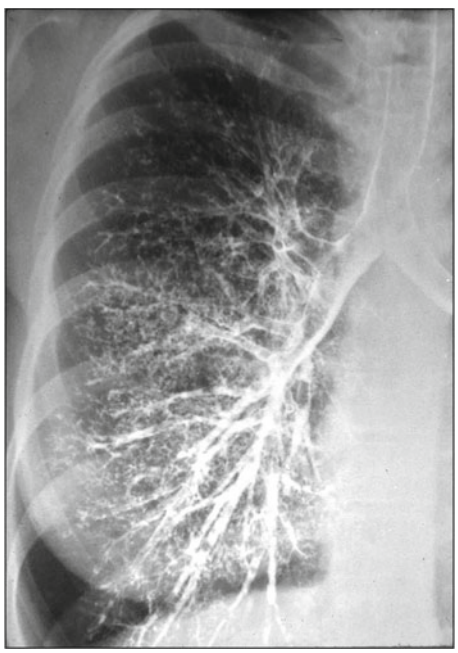

Fig. 42.6 Normal bronchogram. Contrast material is injected into the airway via a bronchoscope and fluoroscopy is performed. Extravasation of contrast material in the pleural space indicates the presence of a bronchopleural fistula (Image courtesy of Stefan Tigges, M.D.)

(technetium-labeled diethylenetriamine penta-acetate), and 99mTc-sulfur colloid has also been described. All of the advanced radiographic techniques mentioned above are now infrequently used with the advent and safety of balloon occlusion of the airway. Historically, bronchography was used for many years with excellent diagnostic accuracy.

Prognosis

In general, there is a high morbidity and mortality associated with bronchopleural fistulas. Mortality generally falls in the range of 20–70%, depending on the underlying disease process. Postoperative fistulas which can be surgically repaired have a lower morbidity and mortality than fistulas related to underlying malignancy or infection. Even with successful intervention, mortality still can be as high as 40%. Death is usually related to a combination of aspiration and recurrent infections (pneumonia, empyema) which may lead to the development of acute respiratory distress syndrome and multiorgan system failure.

Treatment

General Principles

The initial management of any BPF should first address any immediate, life-threatening conditions, such as pleural space contamination, pulmonary flooding, or tension pneumothorax. A chest tube, if not already in place, should be inserted immediately to address these concerns. In complex cases with pleural adhesions and/or loculated hydropneumothoracies, multiple well-positioned and/or image-guided chest tubes may be required. In the case of BPF due to a necrotizing lung or pleural space infection, a trial of antibiotics with adequate drainage should be attempted to decompress the pleural space, allowing time for full lung re-expansion and

healing of the fistula. With severe necrotizing pneumonia, many weeks of antibiotic therapy, nutritional supplementation, patient rehabilitation, and chronic pleural space drainage may be required before contemplating surgery. Although it is tempting to surgically close a fistula, active infection in the lung parenchyma or pleural space can lead to worse outcomes in the acute setting.

Conservative Therapy

Bronchopleural fistulas are very difficult to manage while the patient is on mechanical ventilation. Ventilator-delivered breaths will preferentially flow through the fistula as it represents the lowest point of resistance in the airway. This leads to difficulties with oxygenation and loss of exhaled tidal volumes and subsequent hypercapnia. Limiting airway pressure is an important strategy as continued airflow through the tract delays natural healing. Minimization of positive end expiratory pressure (PEEP), inspiratory flow rate, and tidal volume should be attempted to the extent tolerated by the patient. In large fistulas, selective intubation of the contralateral lung may be necessary to completely cease any airflow through the fistula. High frequency oscillatory ventilation has been studied and found to be slightly more beneficial in patients with a proximal BPF and lack of parenchymal disease.

After initial drainage of the pneumothorax, the chest tube may actually contribute to the persistence of the BPF. In patients with minimal or no residual pneumothorax, suction should be removed and the chest tube placed on waterseal. Keeping the chest tube on suction may have a paradoxical effect by "pulling" the defect open and contributing to the persistence of the BPF. Withdrawal of suction from the chest tubes minimizes airflow through the fistula to allow improved healing of the tract. Installation of a pleural sclerosing agent (talc, bleomycin, etc.) through the chest tube into the pleural space is often attempted as a minimally invasive method for sealing an airleak. The goal is to fuse (pleurodese) the visceral and parietal pleura together, which will either contain the airleak or incite an inflammatory response to close the fistula. In order for this to be successful, the lung needs to completely fill the hemithorax so that there is good apposition between the visceral and parietal pleural surfaces. If a large pneumothorax is present, pleurodesis will not be achieved and the airleak will persist.

Fistula Closure

Conservative measures (as described above) for closure of a bronchopleural fistula are necessary in patients who are poor surgical candidates or have small peripheral defects which do not necessitate more aggressive intervention. In cases where conservative treatment fails, localization of the fistula is paramount in successful closure of the fistula either by semi-invasive (bronchoscopic) or invasive (surgical) management. There have been no large studies describing the optimal treatment or outcomes for bronchopleural fistulas nor does consensus opinion exist to suggest an optimal treatment in any particular situation. Regardless of the cause of the fistula, endoscopic and surgical treatment should not be viewed in isolation; instead, they can be complementary techniques.

Surgical Closure of BPF

If a postoperative BPF is detected within a few days of the patient's original surgery, re-exploration by either VATS or open thoracotomy with closure of the fistula is the recommended approach if the clinical situation allows. The success rate of BPF closure with surgery has been reported to be as high as 80–95%, although this includes the postoperative population that is healthy enough to undergo a major reoperation. There are multiple surgical options described for closure of a BPF: (1) VATS/thoracotomy with direct resection and closure of the stump with intercostal muscle reinforcement or omental flap, (2) trans-sternal bronchial closure, (3) thoracoplasty with or without extrathoracic chest wall muscle transposition, or (4) chronic drainage with chest tube or Eloesser procedure (described below). Sequential operative procedures are often planned in debilitated patients who would not tolerate another major operation. Bronchopleural fistula complicated by empyema is one such circumstance where sequential operations may achieve better success. The pleural cavity is allowed to continuously drain by an empyema tube or an Eloesser procedure. The Eloesser procedure was named after Leo Eloesser, the thoracic surgeon who first described the technique. It involves the creation of a 5-cm opening in the chest wall with resection of 2–3 adjacent ribs and suturing of the skin to the pleural cavity to allow complete continuous drainage of the pleural space. The Eloesser procedure has minimal morbidity even in chronically ill patients and can be used in the acute setting. The patient then undergoes aggressive nutritional support and intensive physical rehabilitation and returns to the operating room once healthy enough to tolerate a second procedure for a thoracotomy with flap closure of the BPF. The details and technical aspects of surgical closure of bronchopleural fistulas are beyond the scope of this discussion. (Please refer to suggested reading at the end of this chapter for additional resources.)

Endoscopic Management of Bronchopleural Fistulas

Role of Brochoscopy

Bronchoscopy is indicated in all patients with a BPF. The bronchoscope has an important diagnostic role in visualiza-

Table 42.3 Endoscopic therapies available for treatment of BPF

Glues and adhesives
Fibrin glue (Coseal)
Polyethylene glycol (FocalSeal-L)
Albumin derivative (Cryolife)
Cyanoacrylate glue (Histoacryl)
Oxidized regenerated cellulose (Surgicel)
Sclerosing agents
Absolute ethanol
Electocautery/laser therapy
Antibiotics
Polidocanol–hydroxypoliethoxidodecane
One-way endobronchial valves
Spiration IBV
Zephyr EBV
Stents
Silicone
Self-expanding metallic stents
Hybrid
Vascular occlusion coils

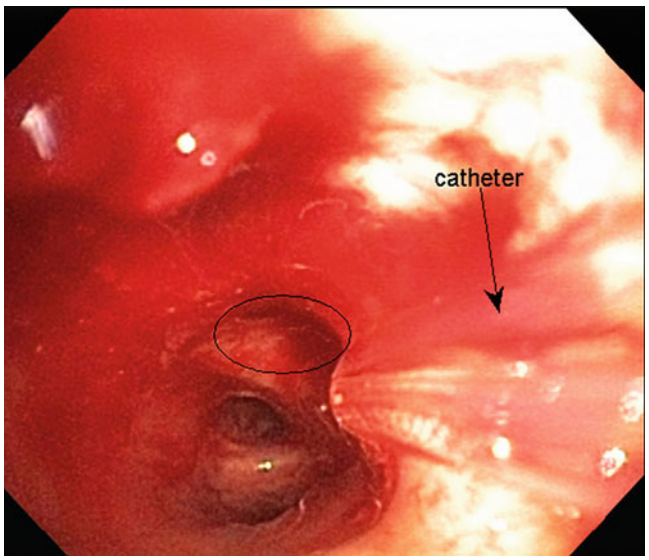

Fig. 42.7 Bronchoscopic view of distal left mainstem bronchus. There is a central bronchopleural fistula (*circled*). Also visible is catheter placed through working channel of bronchoscope approaching the fistula

tion of the airway and/or surgical stump to examine for a central BPF or to identify the involved airway in a peripheral BPF (see "diagnosis" section above). The flexible bronchoscope can also offer a wide range of therapeutic interventions (Table 42.3) as an alternative or adjunct to surgery to treat a bronchopleural fistula. Endoscopic management and surgical repair should not be viewed as competing procedures; rather, they are complementary techniques. For example, treatment may involve two-staged intervention with endoscopic closure performed initially while the patient is acutely ill. Once the patient is more active and nutritionally replete, they can be offered the opportunity to undergo permanent surgical fixation of the fistula. Unfortunately, regardless of procedure, mortality still can be as high as 40% for patients with successfully treated bronchopleural fistulas. This high mortality underscores the critical nature and comorbidities of these patients and needs for further improvements in both endoscopic and surgical techniques.

There are no large controlled trials to document the efficacy or superiority of any surgical or endobronchial closure procedure. No randomized trials have been performed, and recommendations are based on expert opinion and the treating physician's prior experience. The available small studies, case reports, and expert opinion agree that endoscopic closure is safe, well tolerated, and technically feasible in a majority of patients. Success rates vary considerably and are based on small series and isolated case reports. In one of the largest series (40 patients), improvement or resolution of the BPF occurred in 93% of patients treated endoscopically. Repeated procedures are often necessary; the average number of endoscopic intervention required per patient is 2.47 regardless of patient outcome.

Tissue Sealants and Glues

The first report of endoscopic closure of a BPF was by Hartmann in a one-page letter to the editor in Chest in 1977. He reported an IPF patient who underwent a resection of a right upper lobe (RUL) aspergilloma complicated by large BPF. The patient underwent successful closure with occlusion of the effected airway with tissue glue (methyl-2-cyanoacrylate). For centrally located fistulas, visualization by bronchoscopy can help in surgical planning. In nonsurgical candidates, such as described by Hartmann, closure can be attempted by application of sealant material to the airway defect via the bronchoscope. Small (<5 mm) fistulas are more likely to have successful treatment endoscopically, whereas large fistulas (>8 mm) are not suitable for endoscopic closure alone.

In order to close a fistula not seen in the central airways, complete occlusion of the airway (segmental or subsegmental) leading to the BPF will cease airflow through the fistula and allow eventual closure of the airleak. Application of a sealant or glue to "plug" the orifice of the affected airway will therefore cause atelectasis of the distal lung tissue while at the same time occluding airflow through the BPF. Initially, the bronchoscope is fiused to identify the involved segment by systematically inflating a balloon as described above. Once the airway is identified, sealant material can be instilled through a catheter placed through the bronchoscope's working channel. Figures 42.7-42.9 depict the process of applying a sealant to occlude a central BPF.

Multiple types of sealants and glues have been described; however, all initially work by plugging the defect. It typically will take a few minutes for the sealant to form a clot. Cough and forceful respiratory or mechanical ventilation therefore should be minimized for a few minutes after application.

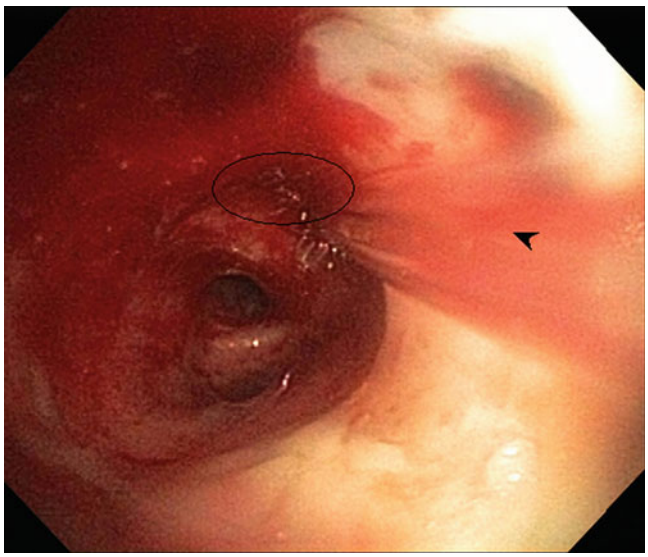

Fig. 42.8 Sealant administration catheter (*arrowhead*) located inside bronchopleural fistula (*circle*)

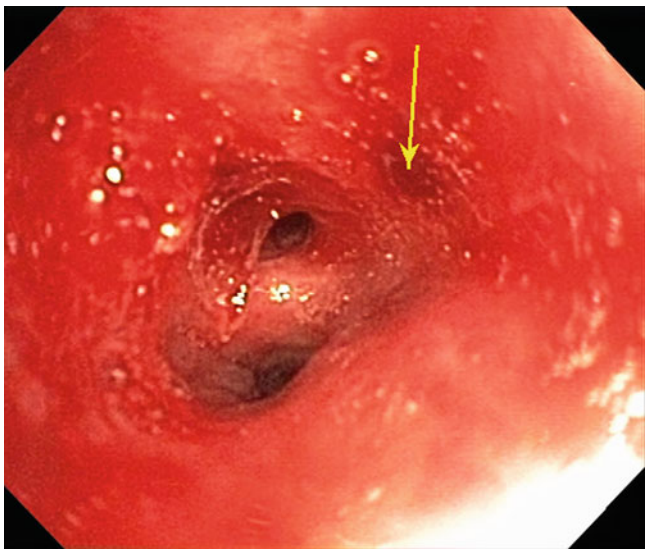

Fig. 42.9 Distal left mainstem bronchus after administration of sealant. Bronchopleural fistula now occluded with bioadhesive sealant (*arrow* denotes prior site of fistula)

The sealant may swell to four times its volume over the next 24 h, completely filling in the fistula or occluding the airway. In the long run, the sealant causes an inflammatory reaction to induce tissue hyperplasia and scarring over the fistula. In animal models, glues induce foreign body granulomas and formation of granulation tissue. The glue is administered through a catheter inserted into the bronchoscope's working channel. Although the glue is injected directly onto a central fistula, it is sometimes necessary to provide a backbone for the glue to adhere. Spongy calf bone, which is both soft and elastic, can be cut and shaped into the form of the fistula. It can then be placed bronchoscopically into the fistula and then covered with fibrin glue.

Peripheral airleaks are more likely to be successfully sealed endoscopically than central fistulas involving the larger airways. Fistulas in central airways are typically larger and involve a prior surgical site. Larger airways also have more secretions which makes it difficult for the sealant to dry and adhere to the airway and fistula. Airflow through the central airways is more robust than in the periphery which makes it harder for the sealant to stay in appropriate position. Even if the sealant is initially successful, it may become dislodged in the future and require repeated administrations.

Fibrin Glue

Fibrin glue is a two-component biologic adhesive which forms a clot when the reagents (fibrin and thrombin) are mixed. It can be injected into the airway through a flexible polyurethane catheter (Duplocath, Baxter Healthcare, Deerfield, IL) which is inserted through the working channel of the bronchoscope. There are a number of commercially available forms of fibrin glue and biologic adhesives; one of the most common being Coseal (Baxter Healthcare, Deerfield, IL) shown in Fig. 42.10. A few mL of concentrated fibrinogen and thrombin is injected simultaneously into the airway through two separate channels in the catheter (Fig. 42.11). When the two compounds mix in the airway, a fibrin clot forms. Care must be taken to not to allow any excess glue in liquid form to come into contact with the bronchoscope. Within a few minutes, the sealant will congeal in the airway and occlude the fistula. Any excess glue, once congealed, should then be removed bronchoscopically to prevent occlusion of the normal airway lumen (Fig. 42.12). Over the next 24 h, the clot will expand and seal off the airway. The clot which forms is gradually reabsorbed, and thus, long-term scarring or damage to the airways is uncommon. Since fibrin is degraded, if the fistula has not healed by the time the fibrin is reabsorbed, then the fistula may recur.

Single-channel catheters are also available for administration of the reagents. Since the compounds harden when they are exposed to each other, it is felt safer to inject them through a dual-chambered catheter running through the working channel rather than sequentially through a single-chamber catheter. If any residual reagent is left in the working channel, when it comes into contact with the other compound, it will clog the working channel. It is recommended not to pull the catheter back through the working channel of the bronchoscope for two reasons: (1) wet fibrin at the end of the catheter can stick to the inside of the bronchoscope, ruining the working channel, or (2) dried fibrin glue adherent to the tip of the catheter can scratch the inside of the bronchoscope also requiring replacement of the working channel. Instead, the catheter and bronchoscope should be removed from the patient as a single unit and the tip of the catheter cut and

Fig. 42.10 Coseal surgical sealant (Coseal, Baxter Healthcare, Deerfield, IL). Dry powder attached to syringe for reconstitution of compound prior to application. The two reagents activate when mixed to form the sealant clot

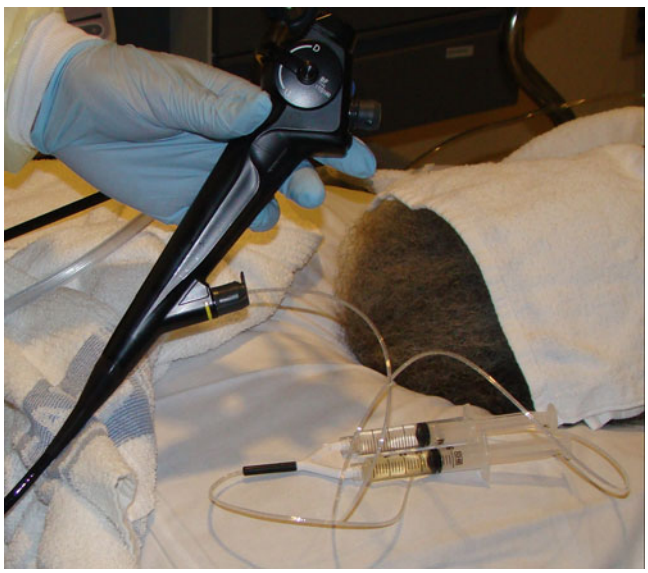

Fig. 42.11 Reconstituted Coseal attached to administration catheter. The catheter is then placed through working channel of bronchoscope

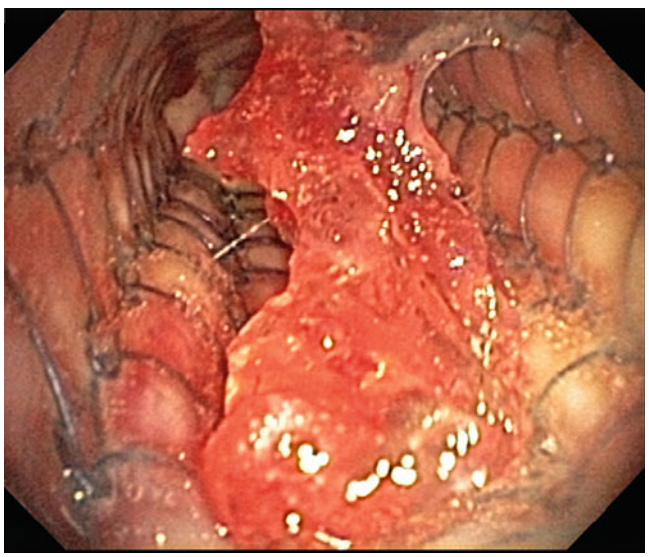

Fig. 42.12 Excessive fibrin glue in airway after administration. Once glue congeals, it can be easily removed with bronchoscope

inspected before pulling the remaining catheter back out through the bronchoscope.

Care must be taken to ensure the injection catheter is far enough away from the bronchoscope so that the sealant will not accidentally come into contact with the scope (Fig. 42.13). Glues which adhere to the scope will cause permanent damage to the lens or exterior of the scope. At no time should suctioning occur while sealant is in the airway. Suctioning of any amount of glue or sealant into the working channel of the bronchoscope will allow the glue to harden within the channel, thus permanently obstructing the working channel. Care must be taken during the initial insertion of the catheter through the working channel of the bronchoscope. Many catheters are thin walled, and a slight kink or bend in the catheter will cause the catheter to tear and sealant to leak into the working channel of the bronchoscope leading to irrecoverable damage. Forcefully injecting the sealant likewise will cause trauma to the catheter leading to leakage. If the sealant hardens within the catheter, the entire catheter must be removed and discarded. It is never a good idea to try to forcefully expel hardened sealant.

Fig. 42.13 Catheter extending through bronchoscope. Tip of catheter placed at distance far enough that administered sealant will not accidentally come into contact with bronchoscope

Fig. 42.14 BioGlue sealant in packaging (Cryolife; Kennesaw, GA). Prefilled syringe for administration of tissue sealant

Other Adhesives and Sealants

Cyanoacrylate glue polymerizes and becomes solid when coming into contact with body fluid or tissue. An early report described two patients with postoperative BPF successfully treated by application of the cyanoacrylate glue through an epidural catheter placed in the working channel of a flexible bronchoscope. One milliliter of glue was instilled directly on the defect.

BioGlue (Fig. 42.14) has been applied surgically to BPFs in patients during VATS or thoracotomy. The adhesive is made from an albumin derivative. It has been helpful for covering lung lacerations or dehiscence at suture or staple lines. Only one patient has been reported to have undergone endoscopic administration of BioGlue by rigid bronchoscopy.

Polyethylene glycol (FocalSeal-L, Focal; Lexington, MA) was recently FDA-approved as a water-soluble polyethylene glycol-based gel. It is "painted" into the airway through the working channel of the bronchoscope. Once activated by light, the sealant forms. This is usually accomplished on external surfaces by the use of a xenon-generated wand which emits light in the spectrum of 440–550 nm. In one selected case report, the sealant was activated by the use of

an autofluorescence bronchoscope which emits a blue light from the scope at 442 nm. This case described the successful closure of a 4-mm dehiscence at a bronchial stump using this method.

Oxidized regenerated cellulose (Surgicel, Ethicon Piscataway, NJ) is a mesh-like sheet of inert material which is typically used to cover a laceration or to control bleeding. It induces fibrinogenesis and mechanically occludes a defect. There is an isolated report of Surgicel used to close a central left mainstem BPF in a patient with advanced lung cancer. A flexible bronchoscope was used to guide the placement of several pieces of Surgicel to mechanically cover the defect. Surgicel does not have any adhesive properties; therefore, to prevent dislodgement of the Surgicel, a Fogarty catheter balloon was inserted nasally and used to pack the Surgicel into the BPF. The Fogarty catheter was then removed 48 h later with complete closure of the fistula and the patient was discharged to home a few days later.

One-Way Endobronchial Valves

Endobronchial valves were originally developed for endoscopic lung volume reduction surgery (LVRS). As a one-way valve, they allow for unidirectional air and secretion flow out of the lung parenchyma but not back in. By preventing airflow back through the affected airway, the airleak is minimized and the fistula may eventually close. Two valves are commercially available and shown in Figs. 42.15 and 42.16. The Spiration IBV (Spiration, Inc. Redmond, WA) is a one-

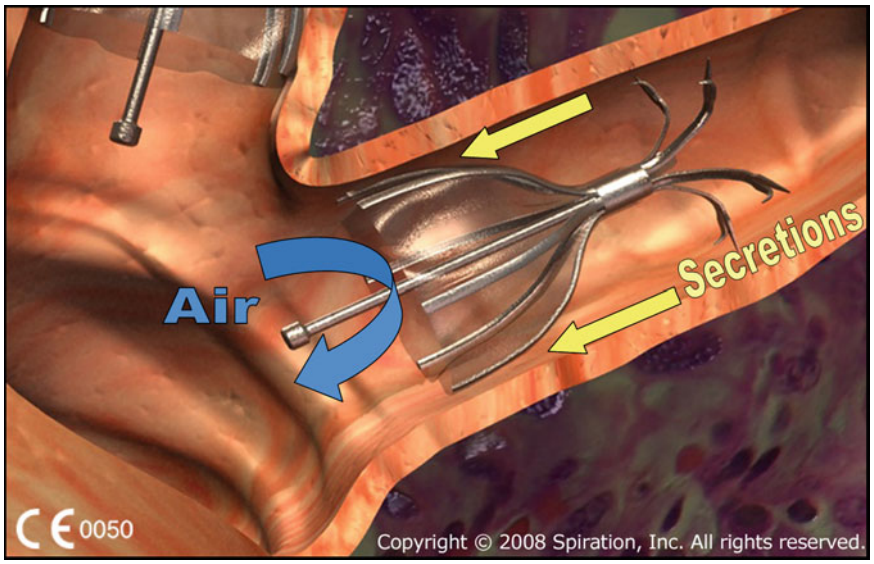

Fig. 42.15 The Spiration IBV is a one-way umbrella-shaped endobronchial valve which is deployed via a flexible bronchoscope. It allows for unidirectional air and secretion flow out of the lung parenchyma but not back in (Printed with permission from Spiration, Inc.)

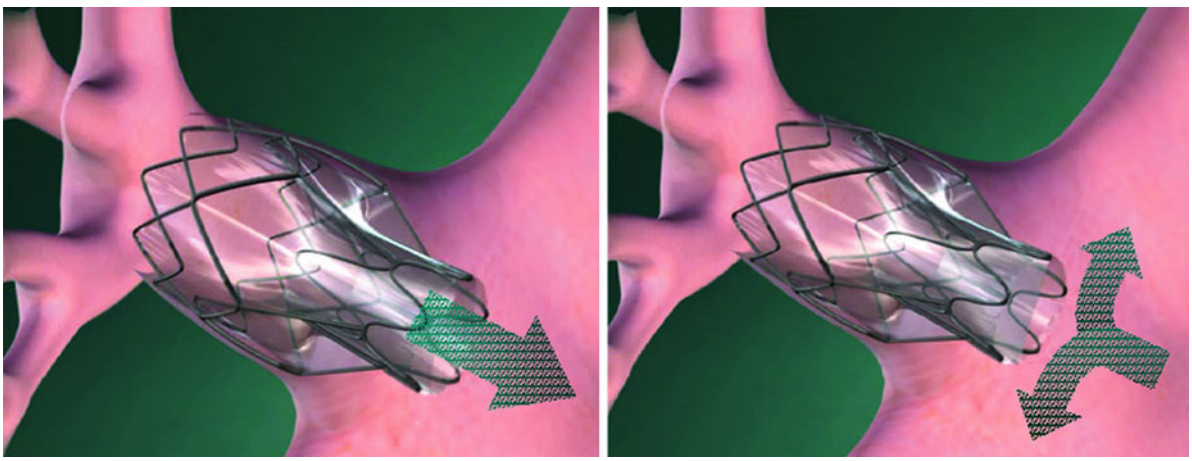

Fig. 42.16 The Zephyr EBV deployed in an airway. It is a self-expanding silicone valve placed via flexible bronchoscope to allow unidirectional air and secretion flow out of lung parenchyma to assist in closure of a BPF. Air flows from parenchyma to central airways during exhalation (**a**, *left*) but cannot flow back through the valve during inspiration (**b**, *right*) (© 2010 Pulmonox. All Rights Reserved)

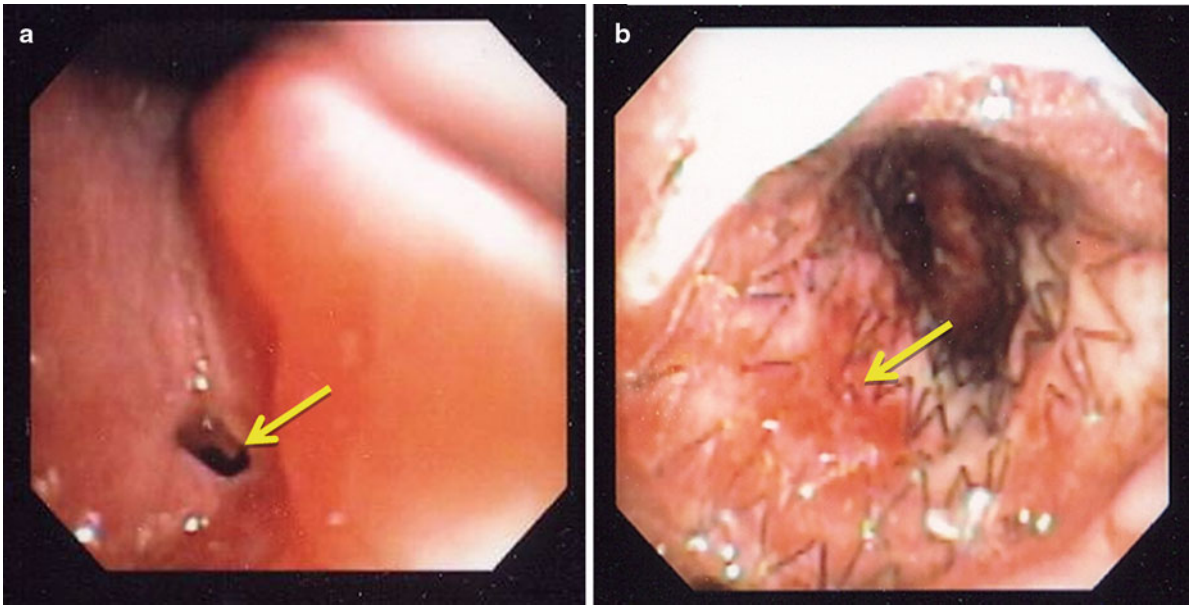

Fig. 42.17 Bronchopleural fistula (*arrow*) in right mainstem covered by a hybrid stent

way valve composed of a nitinol frame and polyurethane umbrella-shaped membrane. It has been approved for compassionate human use in the United States by the FDA since 2008 (HO60002) for prolonged airleaks. The Zephyr endobronchial valve (Pulmonx, Redwood City, CA) is a self-expanding silicone valve with a nitinol backbone. Both valves can be placed through a delivery device which fits through a 2.8-mm bronchoscopic working channel and are designed to be able to be removed once the airleak has resolved. It is recommended to start considering valve removal after 6 weeks to minimize long-term airway complications such as tissue hyperplasia and stenosis around the foreign body (valve).

Travaline et al. published the largest experience with endobronchial valve placement for prolonged airleaks in 2009. One hundred and sixteen Zephyr endobronchial valves were placed in 40 patients (average 2.9 valves/patient) for a variety of etiologies of BPF. Greater than 47% of patients had resolution of the BPF and 45% had improvement of airleak after valve placement. Eight patients had the valves removed at a later date without recurrence of the airleak. Adverse events were minimal and included expectoration of the valve, pneumonia, malpositioning of the valve, and moderate oxygen desaturation. Data for use of the Spiration endobronchial valve for treatment of BPF also supports its compassionate use. As of 2010, a total of 34 patients have been treated with the Spiration IBV for BPF. An average of 3.4 valves are placed per patient with 94% of patients demonstrating a reduction or resolution of the airleak. No complications with placement or removal have been reported. Endobronchial valve placement appears to offer a safe and effective intervention for prolonged airleaks from various causes; however, experience is limited at the current time.

Stents

The first reports of using stents to cover fistulas were described in patients with esophageal to airway fistulas. A majority of these stents were silicone and used to cover the airway defect and prevent further aspiration of gastroesophageal contents and contamination of the airway and lung parenchyma. Patients who already have an esophageal stent placed are at high risk of the stent eroding through the thin posterior membrane of the trachea and bronchus. Cases have been reported of an esophageal stent eroding into the trachea leading to complete airway occlusion and subsequent asphyxiation. As such, airway stents are sometimes placed after an esophageal stent prophylactically to maintain airway patency rather than to cover the defect. Double stenting (esophageal and airway), intended only for palliative purposes, has been reported to improve patient symptoms and possibly improve survival.

A large variety of airway stents are available to cover a bronchopleural fistula. Acutely, stents are placed to provide a mechanical occlusion of the airway defect to prevent further contamination of the airway or pleural space and leakage of air (Fig. 42.17). Over time, however, the stent causes a foreign body reaction leading to granulation tissue formation which hopefully will fill in the fistula with inflammatory tissue. Stents used to cover an airway defect typically have some occlusive material (e.g., silicone or polyurethane) in

order to block the flow of air or secretions through the fistula. Commonly placed stents for this purpose include silicone stents (Tracheobronxane Dumon, Novatech, Westborough, MA), hybrid stents (Aero, Alveolus Inc., North Carolina), and self-expanding metal stents (Ultraflex, Boston Scientific, Natick, MA and Silmet, Novatech, Westborough, MA). Metal stents should be used cautiously in patients with nonmalignant or surgically resected malignant disease. Metallic stents come either uncovered or covered with a thin piece of silicone or polyurethane. As an uncovered stent has openings between the metallic backbone, it will not physically occlude the fistula. The metallic stent will cause an inflammatory response in the airway which will allow the fistula to close over time. Given that these stents will quickly embed into the airway, it is recommended that they be removed as soon as possible in patients with nonmalignant airway disease.

A few specifically tailored bronchial occluding stents have been described. These typically are self-expandable metal stents completely covered in silicone or polyurethane. They are designed for large fistulas from surgical site dehiscence and deployed across a fistula. The proximal end of the stent appears normal and remains in the intact airway. The distal end of the stent is a blind pouch so that there is no direct communication between the airway and the pleural space. These stents have to be custom made and are not widely used at the current time.

Additional Endoscopic Therapies

Vascular occlusion coils (Gianturco or Platinum Coil Vascular Occlusion System, Boston Scientific Co., Fremont) in combination with *n*-butyl-2-cyanoacrylate (Histoacryl; B. Braun Melsungen AG, Germany) have been placed endobronchially to occlude the airway leading to peripheral BPFs. The use of the coil in combination with cyanoacrylate may provide a scaffolding for the sealant and account for the successful closures. At least seven cases have been reported with mixed success using vascular coils.

Sclerosing agents can also be used to induce fibrosis and scarring over of the fistula. Electrocautery or laser therapy can be directly applied to a central lesion or used to "scar" or stenose the airway leading to a BPF. Either therapy, however, can also cause tissue necrosis and expand the size of the fistula. Sclerosis can be accomplished with topical agents. Takaoka et al. described the closure of five patients with a postoperative BPF using absolute ethanol. All fistulas were located in central airway, were less than 3 mm, and were visible by bronchoscopy. Absolute ethanol in 0.1-mL aliquots was injected into the mucosa around the fistula using an injection needle (NM-21 L; Olympus) through the working channel of the bronchoscope. Up to 41 injections were performed during a single bronchoscopy, and one patient required 4 bronchoscopies to complete the closure. All patients had successful closure with range of time from onset to closure of 6 days to 15 months. The ethanol causes rapid dehydration of tissue and induces scar formation. No complications were noted; however, caution must be exercised to prevent excess injection of the absolute ethanol. Excessive injection may cause local tissue necrosis. Spillage of excess ethanol into the airway causes scarring of normal endobronchial mucosa.

Sclerosis may also be accomplished with topical administration of other agents. One report of intrabronchial administration of doxycycline has been described in a 17-year-old man with a BPF that developed as a result of ARDS. Once the involved subsegmental airway was identified, 0.5 g of tetracycline suspended in 25 mL of sterile water was administered through a No. 5 Fogarty catheter. A blood patch was then created using 10 cc of autologous non-heparinized blood injected through the catheter. The airleak resolved and the patient was subsequently able to wean from mechanical ventilation, and a follow-up bronchoscopy 2 weeks later demonstrated almost complete stenosis of the orifice of the treated subsegment. Polidocanol–hydroxypoliethoxidodecane (Aethoxysklerol Kreussler) is mainly used for the sclerosing of veins (varicose or esophageal) but has been used in at least 35 patients with bronchopleural fistulas. When injected (4–5 mL of 2% polidocanol) submucosally around the edges of a fistula, it causes an initial whitish reactive edema followed by hyperemic and thickened tissue (granulation tissue). The procedure is repeated until the fistula fills in and a fibrous scar is permanently formed.

As described earlier, balloon catheter-directed occlusion of subsegmental airways is used diagnostically to identify a peripheral airleak. The balloon, however, could be used therapeutically to block airflow through the fistula. There is at least one report of a nonsurgical patient who had a balloon left in place for weeks to therapeutically occlude a BPF. The patient in this report did not have a favorable outcome.

Conclusion

Bronchopleural fistulas are infrequently seen but have a high mortality even after successful treatment. They occur most commonly after pulmonary resection, however, may be seen in infections, malignancy, or as a complication of cancer treatment. Bronchoscopy is indicated in all patients with BPF and can be helpful in both diagnosis and treatment of the BPF. When conservative measures fail, it is best to evaluate the patient for both endoscopic as well as surgical closure. There is a lack of evidence over optimal treatment method as no large or randomized trials have been performed. Multiple endoscopic therapies have been described on the basis of a few small series and case reports. No one therapy will be preferred in all patients. The clinical scenario as well as patient and physician preference will be the main factors influencing treatment.

Suggested Reading

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Endoscopic Lung Abscess Drainage

43

Felix J.F. Herth

Lung abscess is defined as necrosis of the pulmonary tissue and formation of cavities containing necrotic debris or fluid caused by microbial infection. The formation of multiple small (<2 cm) abscesses is occasionally referred to as necrotizing pneumonia or lung gangrene. Both lung abscess and necrotizing pneumonia are manifestations of a similar pathologic process. Failure to recognize and treat lung abscess is associated with poor clinical outcome. Multiple factors, including the patient's general state of health, the presence of underlying disease, and the virulence of the pathogen responsible, appear to dictate the clinical outcome. Lung abscess was a devastating disease in the preantibiotic era; when one third of the patients died, another one third recovered, and the remainder developed debilitating illnesses such as recurrent abscesses, chronic empyema, bronchiectasis, or other consequences of chronic pyogenic infections. In the early postantibiotic period, sulfonamides did not improve the outcome of patients with lung abscess until the penicillins and tetracyclines were available. Although resectional surgery was often considered a treatment option in the past, the role of surgery has greatly diminished over time because most patients with uncomplicated lung abscess eventually respond to prolonged antibiotic therapy.

Despite the advances made in the care of patients with pyogenic lung infections during the past decades, lung abscess continues to cause morbidity and mortality. The overall incidence of, and mortality from, these conditions has greatly declined since the availability of effective antibiotics and other treatment options.

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Clinical Presentation of Lung Abscess

Most frequently, the lung abscess arises as a complication of aspiration pneumonia caused by mouth anaerobes. The patients who develop lung abscess are predisposed to aspiration and commonly have periodontal disease. A bacterial inoculum from the gingival crevice reaches the lower airways, and infection is initiated because the bacteria are not cleared by the patient's host defense mechanism. This results in aspiration pneumonitis and progression to tissue necrosis 7–14 days later, resulting in formation of lung abscess (Fig. 43.1). Pleuritic chest pain, fevers, cough, hemoptysis, dyspnea, and weight loss are common symptoms at presentation. The incidence remains low with the routine use of antimicrobials.

The first significant step in the study of lung abscess was the cardinal observation of D.T. Smith that the bacteria found in the walls of the abscess at autopsy resembled the bacteria noted in the gingival crevice. He postulated that aspiration of oral bacteria was the mechanism of the infection of lung abscess. The next cornerstone in the understanding of lung abscess came from the demonstration of bacterial synergy, as no single microbe reproduced this disease. Smith was able to produce typical lung abscess with an inoculum containing four microbes (an anaerobic spirochete, *Fusobacterium nucleatum*, *Peptostreptococcus* spp., and a Gram-negative anaerobe, possibly *Prevotella melaninogenica*), multiple cavities, and failure of clinical improvement after 7 days of antibiotics.

Other reports of lung abscess isolates included *Klebsiella pneumoniae*, *Legionella micdadei*, and *Legionella pneumophila* types. Others have reported co-isolation of two or more potential pathogens. *Nocardia asteroides* and *Cryptococcus neoformans* were isolated from a lung abscess in a patient receiving high-dose corticosteroids.

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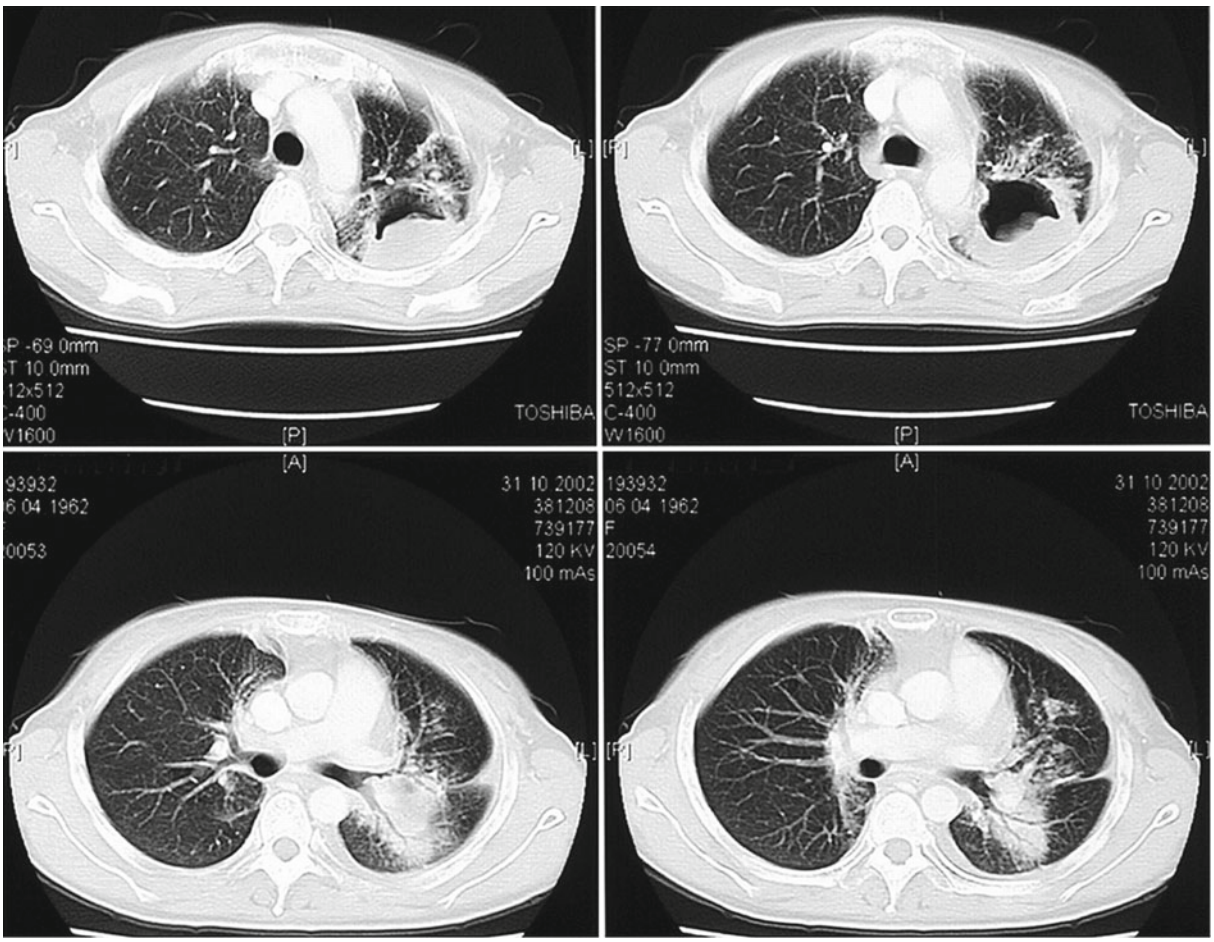

Fig. 43.1 Image of a lung abscess in the segment 6 *left* lower lobe

Management of Lung Abscess

Most patients with primary lung abscess improve with antibiotics, with cure rates documented at 90–95%. Host factors associated with a poor prognosis include advanced age, debilitation, malnutrition, human immunodeficiency virus infection or other forms of immunosuppression, malignancy, and duration of symptoms greater than 8 weeks. The mortality rate for patients with underlying immunocompromised status or bronchial obstruction who develop lung abscess may be as high as 75%.

Medical therapy including antimicrobials remains the cornerstone of therapy. Co-isolation of two or more pathogens from the same specimen may require antimicrobial therapy directed at both potential pathogens. Although the duration of therapy is not well established, most clinicians generally prescribe antibiotic therapy for 4–6 weeks. Expert opinion suggests that antibiotic treatment should be continued until the chest radiograph has shown either the resolution of lung abscess or the presence of a small stable lesion. The rationale for extended treatment maintains that risk of relapse exists with a shorter antibiotic regimen.

In the absence of clinical response, antimicrobial therapy may be combined with tube thoracotomy drainage. Surgical management is considered in cases of large lung abscesses, especially when associated with hemoptysis. Surgery is very rarely required for patients with uncomplicated lung abscesses. The usual indications for surgery are failure to respond to medical management, cases of large lung abscesses, especially when associated with hemoptysis, suspected neoplasm, or congenital lung malformation. The surgical procedure performed is either lobectomy or pneumonectomy.

When conventional therapy fails, either percutaneous catheter drainage or surgical resection is usually considered. Surgical options as video-assisted thoracoscopic surgery (VATS) or open surgery are currently usually reserved for patients with refractory to the antibiotic therapy or acute complications as severe hemoptysis or uncontrolled necrotic pneumonia. However, these approaches, lung resection as the definitive procedure cannot be frequently performed because of septic complications.

These surgical procedures achieved cure rates of 90% but with concomitant mortality rates of 11–28%. In the past two decades, percutaneous catheter drainage has proven effective

in appropriately selected adult and pediatric patients. Endoscopic lung abscess drainage is considered if an airway connection to the cavity can be demonstrated. Success of this treatment represents an additional option other than percutaneous catheter drainage or surgical resection. Antibiotic therapy in combination with diagnostic bronchoscopy and postural drainage where indicated is curative in most cases. If this regimen fails, drainage or resection options are usually considered. Pneumonostomy or cavernostomy with direct drainage (Monaldi procedure) (Fig. 43.2) can achieve this goal but is only possible when the pleural space is obliterated. Lung resection as the definitive procedure cannot be frequently performed because of septic complications. These surgical procedures achieved cure rates of 90% but with concomitant mortality rates of 11–28%.

Bronchoscopy is usually performed for sampling purposes as well as to exclude obstructive lesions within the airways. If airway abnormalities associated with the abscess are present, bronchoscopy can also be undertaken therapeutically for relief of the stenosis. Endoscopic abscess drainage is commonly performed in other organs, such as the pancreas, but rarely in the lungs. It has been estimated that drainage is required in 11–21% of patients with lung abscesses in whom medical therapy is unsuccessful. Commonly in these cases, the first consideration is for percutaneous drainage under CT guidance. This approach may be problematic in patients with coagulopathies, if a significant amount of lung tissue needs to be traversed and if other anatomic structures do not allow for unimpeded access to the cavity. Additionally, there is always a concern for soiling the pleural space with abscess contents. Another consideration if percutaneous drainage appears problematic is for surgical resection of the diseased lung and the abscess.

Endoscopic drainage may be a valuable minimally invasive addition to the armamentarium of the chest physician dealing with patients with a lung abscess. It can be considered in selected patients who have an airway connection to the abscess or in whom an endobronchial obstruction preventing drainage is present. It does not carry the risk of soiling the pleural space and is less invasive and not associated with the loss of lung parenchyma as in a surgical resection.

Endoscopic drainage of parenchymal abscess cavities was first reported by Metras and Chapin in 1954. Three more reports have been published between 1975 and 1988. Altogether, 16 cases with five failures of the endoscopic intervention have been described prior to the largest report, including 42 patients.

Endoscopic Lung Drainage

Flexible bronchoscopy through a nasal approach is performed in a standard fashion. After inspection of the airways, the suspected segment is intubated. Under fluoroscopic control, a guide wire has to be introduced into the cavity through the working channel of a flexible bronchoscope. In case of the successful entering of the cavity, the guide wire will be wind up, which can be observed with the help of the fluoroscopy. In some patients, selective bronchography has to be performed first to identify the airway leading into the cavity. Therefore, a BAL catheter is moved forward in the suspected area, and a water-soluble contrast agent is injected to identify the right segment, which lead to the abscess.

In those patients, the guide wire can be directly introduced through the bronchography catheter. When the guide wire is confirmed to be in place, the catheter and bronchoscope can be removed. A pigtail catheter of 90 cm (Fig. 43.3) in length of at least 7 °F can be slipped over the wire into the cavity (Figs. 43.4,

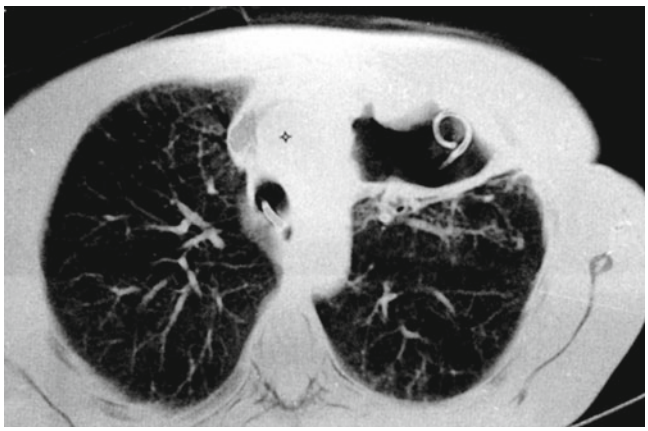

Fig. 43.2 Monaldi procedure

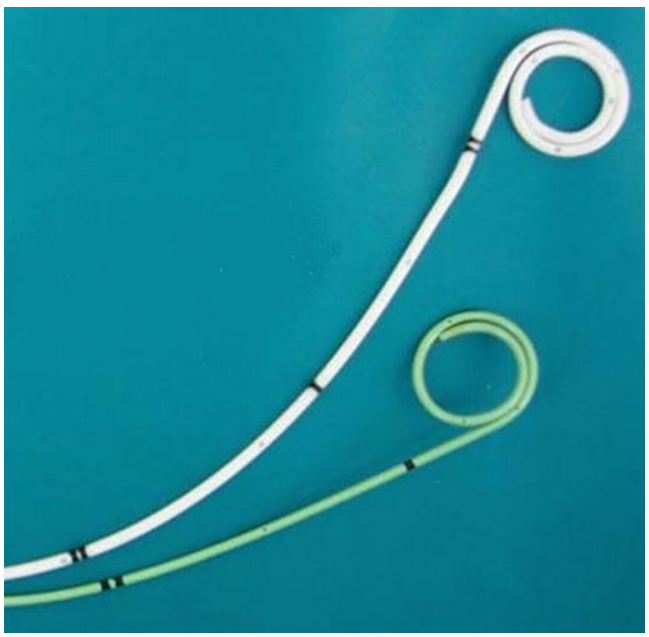

Fig. 43.3 Image of different sizes of a pigtail catheter

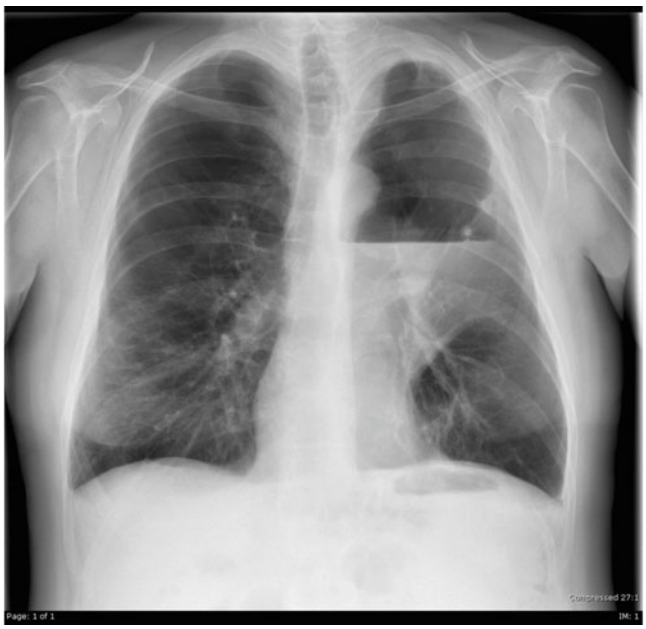

Fig. 43.4 Lung abscess in *left upper lobe* (after 6 weeks with antibiotics)

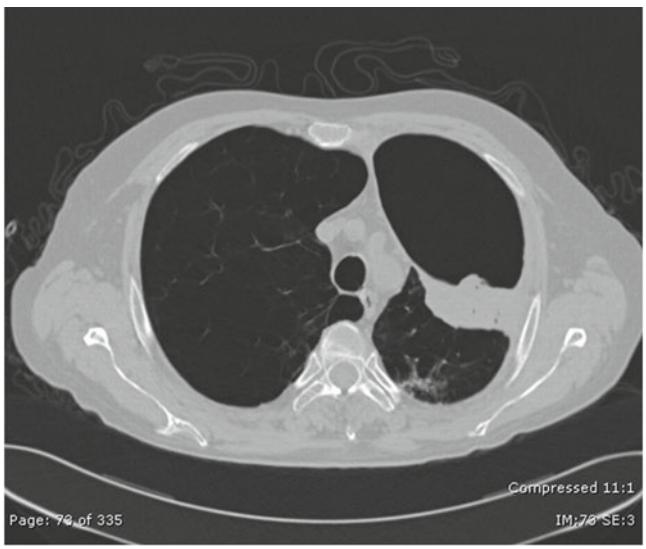

Fig. 43.5 CT from the same patient

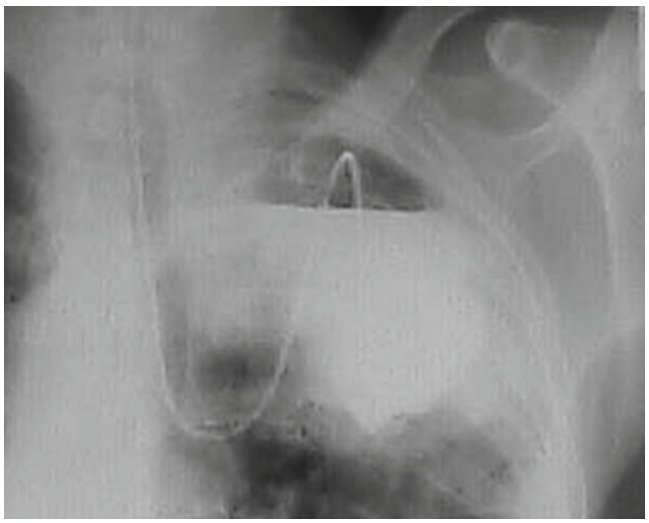

Fig. 43.6 Fluoroscopy with a contrast filling of the cavity after placement of the guide wire

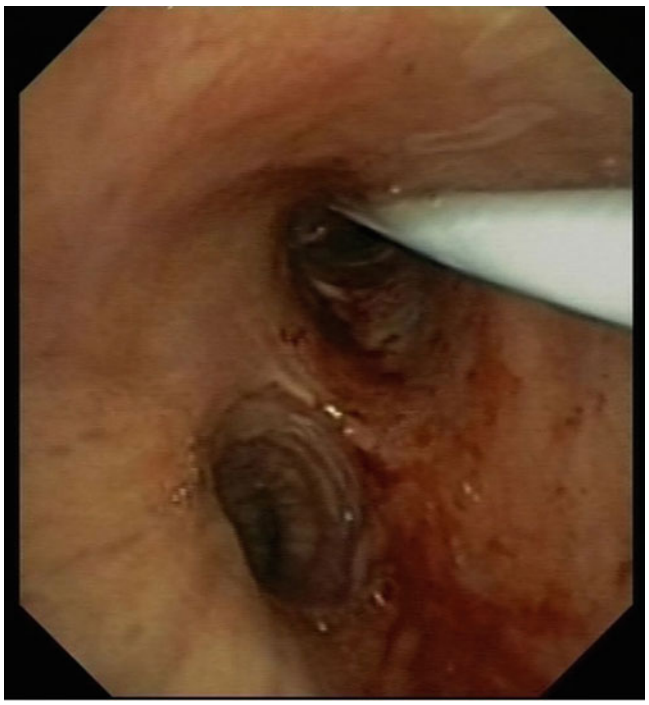

Fig. 43.7 Endoscopic image of the pigtail catheter, entering the *left upper lobe*

43.5, 43.6, 43.7, and 43.8). The correct position has to be checked with an application of contrast medium through the pigtail catheter, followed by the removal of the guide wire. The catheter has to be secured at the nose (Fig. 43.9).

Local Treatment Protocol

It is recommended to flush the abscess cavity twice daily with 80 mg gentamycin in 20 mL of normal saline solution. In cases of documented fungal disease, the addition of 50 mg amphotericin B in 20 mL of normal saline solution was added to the flushes once a day. At all other times, the catheter was open to gravity. All patients continued with their previously established antibiotic therapy. In the trial, 42 patients were included in this study. Catheter placement was successful in 38 patients and led to successful therapy after a mean of 6.2 days of treatment (range, 3–21 days). Two patients required transient ventilation after catheter placement; there were no other complications. The trial showed that endoscopic lung abscess

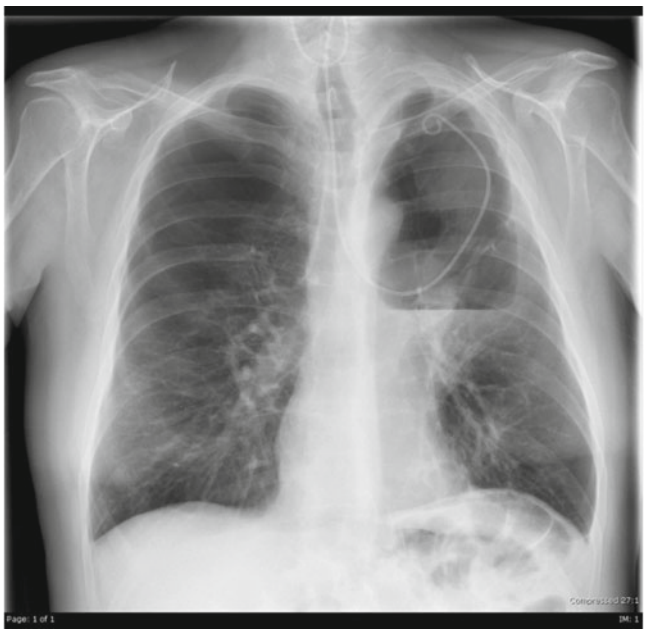

Fig. 43.8 The pigtail in place

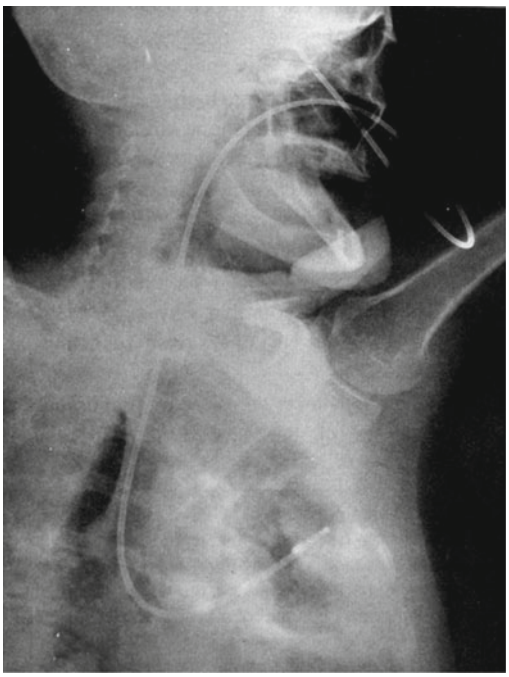

Fig. 43.9 The way of the catheter

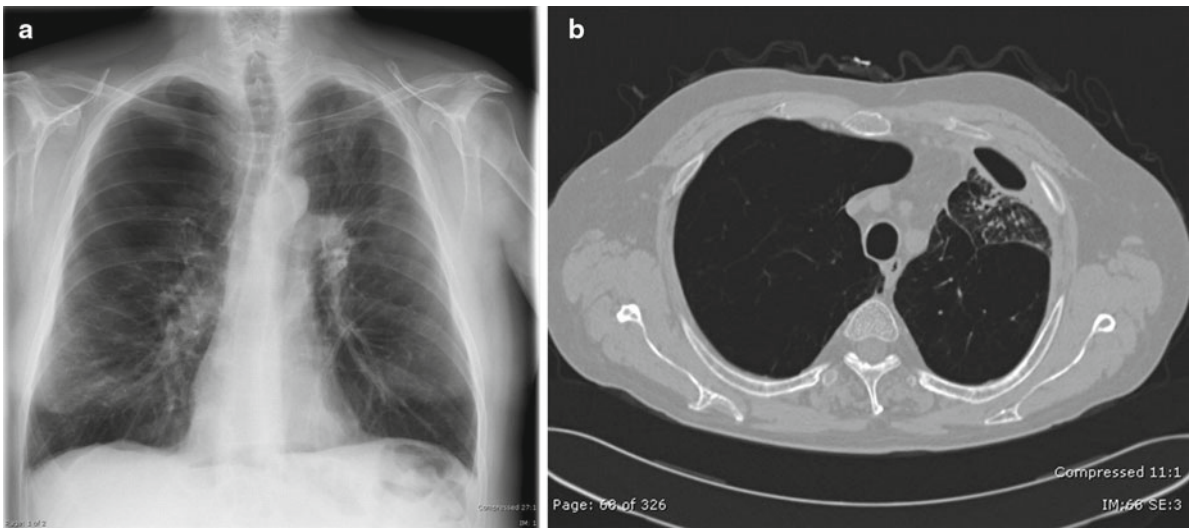

Fig. 43.10 (**a**) X-ray and (**b**) CT after 6 weeks of rising the pigtail twice/day and 6 weeks follow-up

drainage in selected patients in whom antibiotic therapy fails is feasible and successful in experienced hands (Fig. 43.10a, b).

Conclusion

In conclusion, experience with endoscopic abscess drainage is excellent in selected patients in whom conventional therapy fails. It seems an alternative to percutaneous drainage in patients who are coagulopathic, have airway obstruction, or have a fairly central abscess if an airway leading to the abscess can be demonstrated.

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Management of Massive Hemoptysis

44

Andrew R. Haas

Introduction

The expectoration of blood is known as hemoptysis, derived from the Greek "haima" for "blood" and "ptysis" for "a spitting." Massive hemoptysis, which comprises approximately 5% of all hemoptysis cases, is variably defined as the expectoration of blood greater than 100–500 ml over a 24-h period. It is a medical emergency and often a sign of a serious underlying medical condition. With a mortality rate as high as 75%, death is due to acute airway obstruction and hypoxemic respiratory failure, not exsanguination, as commonly misperceived. Total airway dead space measures approximately 150 ml; therefore, conducting airways can become obstructed with minimal bleeding if a patient is unable to clear blood effectively from their central conducting airways. This chapter will review the causes, diagnostic modalities, and management strategies of massive hemoptysis.

Anatomy

The lungs have a dual blood supply – the pulmonary arterial circulation participates in gas exchange, while the bronchial arterial circulation supplies the pulmonary parenchyma. The pulmonary arteries arise from the right ventricle, branch into lobar arteries, and eventually form the fine alveolar capillary interface which participates in gas exchange. The pulmonary arterial circulation is a low-pressure, low-resistance system with significant capacitance to accommodate increased blood flow without a marked pressure increase. The pulmonary parenchyma nutrient supply is provided by the bronchial arteries arising typically from the aorta and occasionally from an intercostal artery. In contrast to the pulmonary arterial circulation, the bronchial artery circulation is a high-pressure system with peribronchial plexi surrounding the airway and small penetrating arteries supplying the bronchial mucosa via submucosal plexi. Due to the pressure difference between these two systems, massive hemoptysis can be more rapid and life threatening when originating from the bronchial rather than the pulmonary arterial circulation. Furthermore, in certain inflammatory and infectious pulmonary conditions, parasitized intercostal arteries can form which can be the massive hemoptysis bleeding source.

Differential Diagnosis of Massive Hemoptysis

Historically, tuberculosis (TB), bronchiectasis, and lung abscess were the most common causes of massive hemoptysis and accounted for approximately 90% of cases. Due to modern medicine developments, the etiologic spectrum has evolved. Widespread antibiotic use has significantly reduced the prevalence of infectious disease causing massive hemoptysis. When a patient presents with massive hemoptysis, one should think of several major etiologic categories as the diagnostic and management plan are being implemented: infection, neoplasm, autoimmune disorders, cardiac and vascular abnormalities, iatrogenic, trauma, and other entities.

Infections

Prior to antituberculous medical therapy in the mid-twentieth century, TB and its sequelae were the most common cause of massive hemoptysis. While massive hemoptysis from TB can still be seen, the rising incidence of nontuberculous mycobacterial infection (*M. abscessus*, *M. kansasii*, *M. avium* complex) now contributes more to massive hemoptysis than TB. The most common reason for massive hemoptysis in these infections is bronchiectasis.

Bronchiectasis is a sequela of acute and chronic infectious and inflammatory processes and is characterized by abnormal bronchial wall thickening with luminal dilatation that

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manifests clinically as daily cough with sputum production and airflow obstruction. Repeated bacterial infections, particularly with *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and chronic neutrophilic airway inflammation are a bronchiectasis hallmark that can lead to hypertrophied and tortuous bronchial arteries, systemic-pulmonary vascular anastomoses, or parasitized intercostal arteries. Rupture of these vessels can cause massive, rapidly fatal hemoptysis.

Fungal infections have become an increasingly common massive hemoptysis source, particularly in two patient populations: those with preexisting cavitary lung disease and profoundly immunocompromised patients (e.g., hematopoietic stem cell transplantation). Patients with cavitary lung disease can develop intracavitary fungal colonization and mycetoma formation (e.g., aspergilloma). Bronchial and intercostal artery dilation and hypertrophy can be dramatic surrounding these cavities. It is estimated that 50–90% of aspergilloma patients can have hemoptysis at some course during their disease. Massive hemoptysis tends to be uncommon in immunocompromised invasive fungal infections until neutrophil count recovery begins after a prolonged neutropenic period. This neutrophil infiltration promotes a very rapid and brisk inflammatory response which can lead to vascular disruption and massive hemoptysis.

Other pulmonary infections can cause massive hemoptysis. Lung abscesses due to polymicrobial and anaerobic bacteria or necrotizing pneumonias caused by *Staphylococcus* species, *Klebsiella pneumoniae*, or *Legionella pneumoniae* can cause massive hemoptysis. Recently, community-acquired methicillin-resistant *S. aureus* has been a massive hemoptysis source due to its tendency to cause parenchymal necrosis and cavitation.

Neoplasms

Any type of bronchogenic carcinoma can cause hemoptysis which can occur either at presentation or during the malignancy course. Due to its more frequent central location, squamous cell histology can lead to massive hemoptysis more frequently than adenocarcinoma, small cell carcinoma, or large cell carcinoma. Endobronchial and central tumor location and tumor cavitation may be associated with a higher hemoptysis incidence. New targeted, chemotherapeutic agents (e.g., bevacizumab) have ushered in an era where dramatic cavitary responses can predispose to massive hemoptysis.

Any endobronchial or intraparenchymal metastatic tumor to the lung can cause massive hemoptysis. Melanoma, lung, colon, breast, or prostate cancer has a tendency to form endobronchial metastases, while renal cell, thyroid cancer, and sarcomas tend to form parenchymal metastases that are prone to cause massive hemoptysis.

Autoimmune

Autoimmune disease can cause massive hemoptysis through a variety of mechanisms. Diffuse alveolar hemorrhage (DAH – Table 44.1) should always be considered when a patient presents with massive hemoptysis. Interestingly,

Table 44.1 Massive hemoptysis etiologies

Infection
Tuberculosis/mycobacterial infection
Bronchiectasis
Fungal infections (primary or mycetoma)
Lung abscess
Paragonimiasis
Hydatid cyst
Necrotizing pneumonia
Septic emboli
Neoplasm
Lung cancer (non-small or small cell)
Pulmonary carcinoid
Endobronchial metastases
Parenchymal metastases
Autoimmune
Diffuse alveolar hemorrhage
ANCA-associated granulomatous vasculitis (formerly Wegener's granulomatosis)
Goodpasture syndrome
Microscopic polyangiitis
Polyarteritis nodosa
Systemic lupus erythematosus
Rheumatoid arthritis
Systemic sclerosis
Cardiac/vascular
Arteriovenous malformation
Mitral stenosis
Pulmonary embolism/infarct
Congenital heart defects
Pulmonary hypertension
Aortic aneurysm
Bronchoarterial fistula
Congestive heart failure (systolic and/or diastolic)
Pulmonary vein stenosis following atrial fibrillation ablation
Iatrogenic
Bronchoscopy
Transthoracic needle aspiration
Transbronchial biopsy
Pulmonary artery catheterization
Tracheo-innominate artery fistula
Radiotherapy
Targeted chemotherapeutic agents (e.g., bevacizumab)
Trauma
Blunt chest trauma
Penetrating chest trauma
Other
Pseudohemoptysis
Bone marrow transplantation

patients with DAH can have profound hypoxemic respiratory failure with little to no hemoptysis. Other autoimmune diseases particularly lupus, rheumatoid arthritis, and systemic sclerosis can develop DAH and hemoptysis associated with rapid hypoxemic respiratory failure.

Cardiovascular Disease

There are a variety of cardiac and vascular hemoptysis sources (see Table 44.1). Among the primary cardiac hemoptysis sources, elevated pulmonary venous pressure leads to venous dilation and varix formation which may rupture and bleed during sudden pulmonary venous pressure increases (e.g., systolic or diastolic failure, cough, Valsalva). Hemoptysis is generally self-limited but can be rarely severe. In a similar fashion, localized pulmonary venous hypertension from pulmonary vein stenosis following atrial fibrillation radiofrequency ablation can result in massive hemoptysis. Similar to their tendency to bleed in other anatomic locations, pulmonary arteriovenous malformations can bleed spontaneously and cause massive hemoptysis.

Iatrogenic Causes

A number of invasive procedures may be complicated by massive hemoptysis. Massive hemoptysis during bronchoscopy is rare and usually occurs in the setting of platelet dysfunction, thrombocytopenia, or coagulopathy when transbronchial biopsies are performed. Pulmonary artery catheter flotation may cause pulmonary artery rupture and has been reported to have a mortality rate greater than 50%. Avoiding balloon overinflation and insuring balloon deflation prior to catheter advancement can help avoid this potentially lethal complication.

A tracheal-innominate artery fistula (TIF) may develop in the chronic tracheostomy setting. A low tracheal insertion (below the recommended first to third tracheal rings) or a high innominate artery may predispose to TIF formation. One potential clue of TIF is the "sentinel bleed" – a small amount of fresh tracheal blood that appears usually 2 weeks or more after tracheostomy placement that can be a harbinger of a catastrophic, fatal bleed.

Massive hemoptysis is a known thoracic radiotherapy complication which more commonly occurs with endobronchial brachytherapy than external beam radiotherapy. Bleeding usually occurs from bronchovascular necrosis and erosion.

Trauma

Massive hemoptysis may occur in the chest trauma setting. Blunt trauma can cause airway rupture with associated injury to the pulmonary or bronchial vasculature. Alternatively, fractured ribs can cause a lung laceration with hemoptysis and/or hemothorax. Similarly, penetrating trauma can directly lacerate the pulmonary, bronchial, or other major vascular structures, causing hemoptysis and/or hemothorax.

Other

An important massive hemoptysis source to always consider is "pseudohemoptysis" or bleeding from a source other than the lung. Epistaxis and hematemesis are two common scenarios that can mimic hemoptysis and patients may be unable to differentiate the bleeding source. Therefore, if pseudohemoptysis is suspected, involving an otolaryngology or gastrointestinal specialist in the patient's care can be crucial. Bone marrow transplant recipients can develop massive hemoptysis that is not necessarily temporally related to the transplant and is likely due to a microvascular chemotherapeutic injury.

Diagnostic Approach

History and Physical Exam

Though rarely able to diagnose the massive hemoptysis etiology in isolation, the basic history and physical exam can provide initial clues as to underlying etiology, but taking a history should not delay urgent interventions. Physicians should elicit any recent history of infectious symptoms. Particular attention should focus on eliciting any prior underlying lung or cardiac disease, any prior occupational or tobacco exposures, any connective tissue disease associated symptoms, or any family lung or bleeding disorder history.

If the patient is stable enough for examination, the physician should note the presence of any pulmonary exam findings that might indicate laterality of the massive hemoptysis source. Evidence of congestive heart failure or a malignancy can guide diagnostic evaluation implementation and provide an impression of how quickly the patient requires definitive management.

Laboratory Studies

Initial tests should include a complete blood count, coagulation studies, blood urea nitrogen, creatinine, and urinalysis. These study results may provide clues to the presence of any underlying systemic disorders (e.g., coagulopathy, autoimmune pulmonary-renal syndromes). Serologies can be sent to evaluate for a suspected pulmonary-renal syndrome. Sputum and blood cultures should be performed to look for pathogenic organisms when an infectious source is suspected.

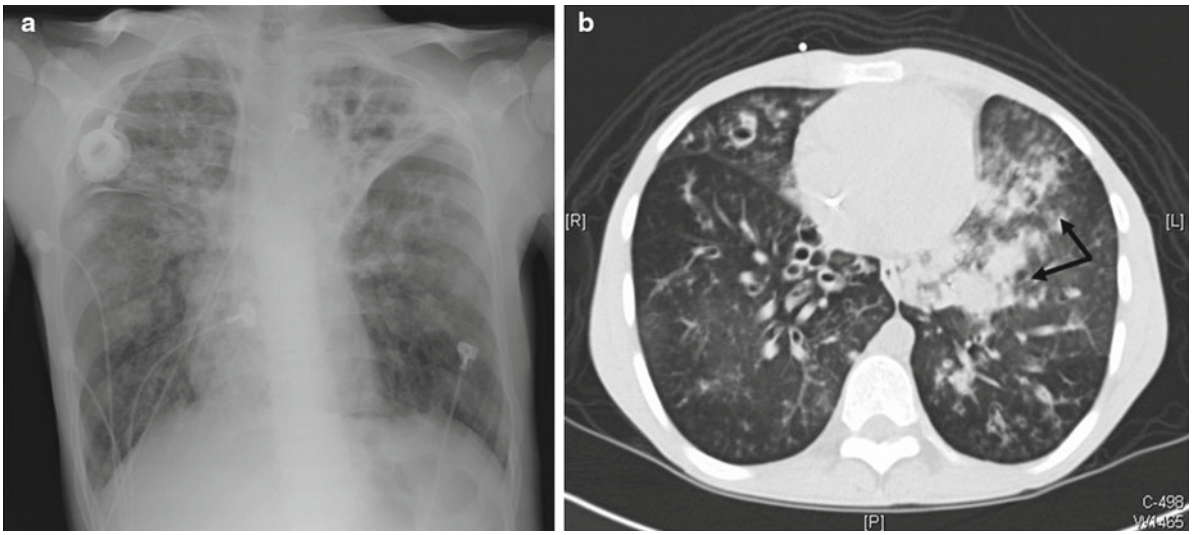

Fig. 44.1 A 25-year-old cystic fibrosis patient presented to the emergency department after 650 ml of bright red blood hemoptysis over a 10-min period. The hemoptysis spontaneously reduced without intervention to blood streaked sputum. A plain film was obtained which demonstrated stable bilateral *left* greater than *right* chronic bronchiectatic changes (**a**). As the patient had stabilized, a CT scan was obtained which demonstrated new *left* lower lobe ground-glass opacities and infiltrates (*arrows*) compared to a CT scan from 3 months prior to the current scan. (**b**) These infiltrates likely represented aspirated blood and localized the bleeding to the left lung which could not be appreciated on the CXR. The patient proceeded to BAE with attention to the left lung vasculature which localized a dilated, tortuous bronchial artery with a small blush which was embolized. In addition, a parasitized internal mammary branch was localized terminating in the vicinity of the bronchial artery and was embolized

Radiographic Studies

Radiographic studies form the diagnostic evaluation backbone in massive hemoptysis. A guiding principle is to localize a lesion upon which intervention may be performed if necessary. The standard chest radiograph (CXR) is (Fig. 44.1a) an important initial tool that can identify pathologies like cavitary lesions, tumors, lobar or alveolar infiltrates, infarcts, and/or mediastinal masses. However, the standard CXR false-negative rate can be up to 20–40%.

Computed tomography scan (CT scan) greatly enhances (Fig. 44.1b) the radiographic evaluation due to its enhanced sensitivity compared to CXR. Contrast enhancement can detect pulmonary emboli, AVMs, or aneurysms. Moreover, multifocal CT scan abnormalities may help identify bleeding laterality. Two major limitations to CT scan are (1) the time required to obtain the study and (2) supine positioning which can impair airway clearance in the event of ongoing bleeding. Therefore, in rapidly progressive, life-threatening hemoptysis, definitive intervention should not be delayed for a CT scan.

Management

Management of massive hemoptysis and the use of particular therapeutic modalities are influenced by the underlying hemoptysis etiology and local expertise and resources. Management should be multidisciplinary in nature, involving pulmonary/critical care physicians, cardiothoracic surgeons, and interventional radiologists.

The bronchoscope is a vital tool in massive hemoptysis diagnosis and management. Though the flexible bronchoscope is often utilized due to its availability, accessibility, and physician comfort, it can be limited by its minimal suction capacity which rapidly impairs visualization. Rigid bronchoscopy allows simultaneous large bore suction, airway maintenance, and ventilation and is the preferred modality in life-threatening hemoptysis. Rigid bronchoscopy can be limited by physician experience and inability to access beyond the trachea and mainstem bronchi. Consequently, rigid and flexible bronchoscopies are often combined to achieve optimal bleeding evaluation and control.

Acute Management

The massive hemoptysis therapeutic cornerstone begins with assuring a secure airway and attempting to isolate the bleeding source. Since the optimal airway clearance mechanism in the setting of active bleeding is the patient's own cough reflex, endotracheal intubation should ***NOT*** be a reflex reaction to massive hemoptysis. Allowing the patient to clear their own airway is more effective than any mechanical intervention. Patients should be admitted to and monitored very closely in an intensive care unit (ICU). Endotracheal

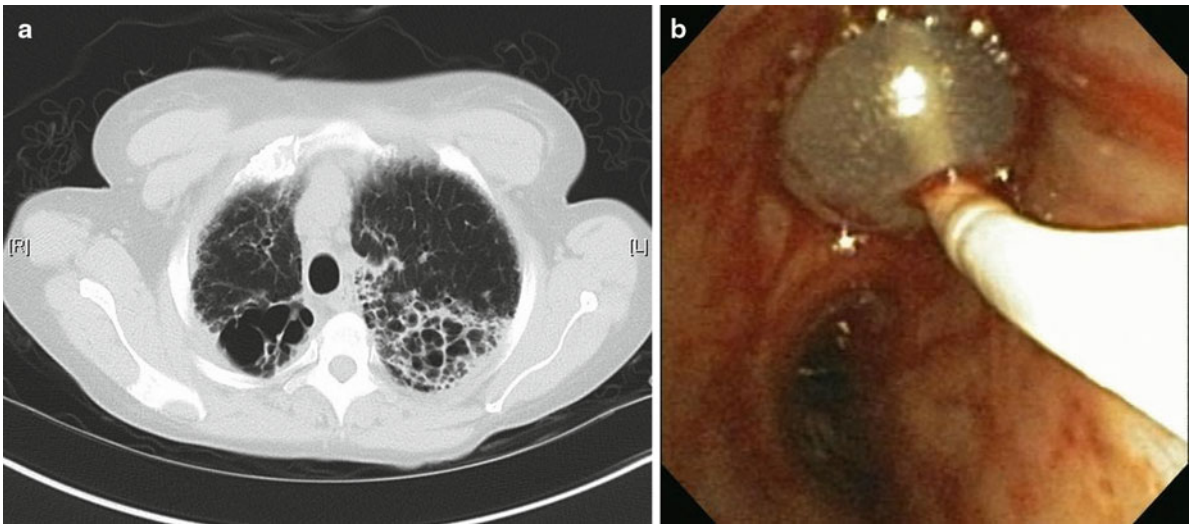

Fig. 44.2 A stage IV sarcoidosis patient with bilateral upper lobe cystic and bronchiectatic changes presented to the emergency department with roughly 400 ml of massive hemoptysis. The bleeding persisted but in significantly smaller volumes. A CT scan showed biapical cystic and bronchiectatic changes but could not identify bleeding laterality (**a**). The patient underwent flexible bronchoscopy with minimal sedation that demonstrated right tracheobronchial tree blood suggestive of a *right*-sided bleeding source. Before the procedure was complete, the patient had a coughing paroxysm that initiated active brisk right upper lobe bleeding. A Fogarty embolectomy catheter balloon (Edwards Lifesciences, Irvine, CA) was advanced into the right upper lobe and inflated to tamponade the bleeding source. The balloon remained inflated for 15 min to allow clot formation and hemoptysis cessation. The procedure was completed and the patient taken to interventional radiology for BAE

intubation should proceed if a patient cannot clear the bleeding or develops progressive respiratory distress or hypoxemia. Intubation with large bore endotracheal tubes (ETT, e.g., 8.5- or 9-mm diameter) is recommended to facilitate suctioning and to allow bronchoscope insertion. If the patient has ongoing large volume hemoptysis, the patient should proceed directly to rigid bronchoscopy to allow simultaneous large volume suctioning, ventilation, mechanical temporizing maneuvers (balloon exclusion), and/or coagulation modalities (if needed).

As mentioned, the second management cornerstone is to ascertain the bleeding source and to determine its laterality (if present – Fig. 44.2a). Blood spillage into the unaffected normal lung can either obstruct the airway with clot or prevent alveolar gas exchange. Therefore, preventing blood entry into the uninvolved lung in unilateral hemoptysis is a tantamount priority. The initial method to accomplish this goal is to place the patient in the lateral decubitus position with the bleeding source lung down, thereby minimizing blood soilage into the uninvolved lung.

Once the decision for endotracheal intubation is made, physicians should be prepared to provide airway clearance as all natural airway protective mechanisms are obliterated upon endotracheal intubation induction. If bleeding laterality is known based on imaging studies, the initial ETT insertion should be advanced into the uninvolved lung far enough to allow endotracheal balloon inflation in the mainstem bronchus to protect it from continued blood soilage. If available, selective lung intubation with direct bronchoscopic visualization may be technically easier.

Two other mechanical approaches to isolate bleeding involve using balloon-occlusion devices. Upon intubation, a bronchoscope can determine the bleeding source and a Fogarty embolectomy balloon can be passed alongside the bronchoscope in the ETT to the site of interest and inflated to occlude the airway (Fig. 44.2b). As expeditious hemoptysis control and contralateral airway protection is the goal, the right or left mainstem airway can be occluded with either a 6 or 7 French (F) embolectomy balloon. The balloon is introduced into the desired airway by rotating the head to the opposite direction of the desired mainstem airway (e.g., for left mainstem balloon placement, turn the head to the right). By not passing the balloon through the bronchoscope working channel, one can occlude the bleeding airway and retain the bronchoscope visualization and suction capacity. This technique is only a temporizing measure as there is no reliable method to anchor the balloon in position to prevent migration. However, temporary occlusion of the bleeding airway may allow enough time for clot formation and hemostasis or evaluation and initiation of a definitive procedure.

In contrast, a bronchial blocker can remain fixed in place for a prolonged time period (Fig. 44.3). A specialized ETT adaptor allows for bronchial blocker insertion and fixation via a separate port from the ventilation port. Once in place, the balloon can be inflated and then locked into position with the ETT adaptor. Insertion requires a small-diameter

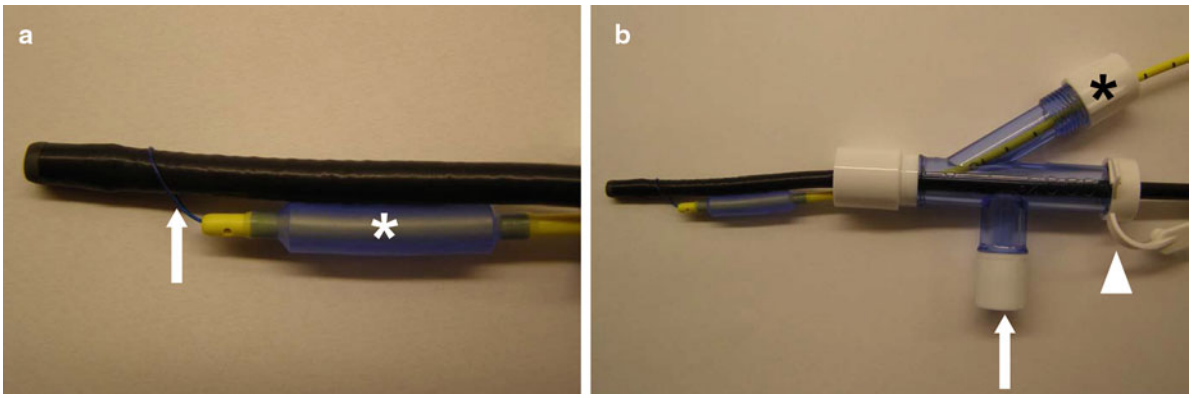

Fig. 44.3 The endobronchial blocker consists of two main components, the bronchial blocker balloon and a three-way ETT adaptor. (**a**) The bronchial blocker balloon (*asterisk*) has a monofilament loop (*arrow*) at the distal tip that allows the scope to pass through. (**b**) The three-way ETT adaptor consists of the following ports: (1) a ventilation port (*arrow*), (2) a bronchoscopy access port (*arrowhead*), and (3) a bronchial blocker balloon access port (*asterisk*). To place the bronchial blocker balloon, the scope is advanced through the bronchoscopy access port to the level of the bronchial blocker balloon access port as the monofilament loop is advanced through the port. The bronchoscope is advanced through the monofilament loop and then into the airway of interest. Since the bronchial blocker is ensnared around the bronchoscope, the bronchial blocker can be advanced over the scope into the airway of interest and inflated. The proximal port of the bronchial blocker port contains a compression fitting that is tightened on the bronchial blocker catheter to lock it into place

bronchoscope to fit through the loop at the distal end of the blocker. The bronchial blocker balloon-occlusion method is also a temporizing measure prior to a definitive procedure. With either of these balloon-occlusion methods, the balloon must be deflated every several hours to prevent mucosal and airway ischemia from the hydrostatic pressure exerted by the balloon. This evaluation should be done ideally under bronchoscopic vision in the event of continued brisk bleeding for which the balloon would need reinflation.

Finally, double-lumen ETT intubation allows independent lung ventilation and toileting, but accurate tube placement can be difficult and time consuming. Limitations such as narrow individual lumen diameter predisposed to blockage, the need for specialized suction catheters, and neuromuscular paralysis limit the role for double-lumen tube in massive hemoptysis management.

Though supporting data is anecdotal, iced saline lavage, topical epinephrine, vasopressin, thrombin, or a fibrinogen-thrombin composite can be attempted via the bronchoscope to create vasoconstriction and hemostasis. Laser therapy, electrocautery, or cryotherapy can also be performed if a bleeding mucosal lesion is visualized during bronchoscopic examination. Other measures reported include placement of endobronchial silicone spigots or surgicel packing into bleeding airways to create hemostasis while more definitive measures are considered.

If a TIF is suspected, immediate cardiothoracic surgery or otorhinolaryngology consultation must be initiated. Until surgical repair is under way, a few temporizing maneuvers can be performed to tamponade the arterial lesion: (1) tracheostomy tube cuff hyperinflation and (2) tracheostomy tube exchange with standard oral endotracheal intubation followed by finger insertion into the tracheostomy stoma with anterior pressure against the sternum to tamponade bleeding.

Clot Extraction

Death from massive hemoptysis ensues from hypoxemic respiratory failure due to central airway obstruction from organized clot. If massive hemoptysis progresses to hypoxemic respiratory failure, bleeding source control is vital, but clot extraction to improve ventilation can be required. If local expertise allows for rigid bronchoscopy, the patient can be ventilated, clot can be extracted with large bore suction, and the source of bleeding can be addressed with the aforementioned modalities. Should this expertise or time not be available, several maneuvers can be performed with flexible bronchoscopy to remove clot. First, simply advancing the scope into the clot burden, activating and maintaining suction while the scope is withdrawn from the airway occasionally can remove obstructing clot. If this fails, an embolectomy balloon can be advanced down the central airway to distal regions of the clot, inflated, and pulled back to the scope while suction is being activated and the scope withdrawn from the airway. Other commonly used extraction devices such as forceps, three-prong graspers, snares, or baskets rarely can remove fresh clot as these instruments just cut or pass through the clot without grasping it for removal. If available, cryotherapy is a very effective modality to extract large clot burdens. The probe is advanced onto the clot and activated which freezes the clot to the probe. The scope is then removed en bloc while cryotherapy activation is maintained

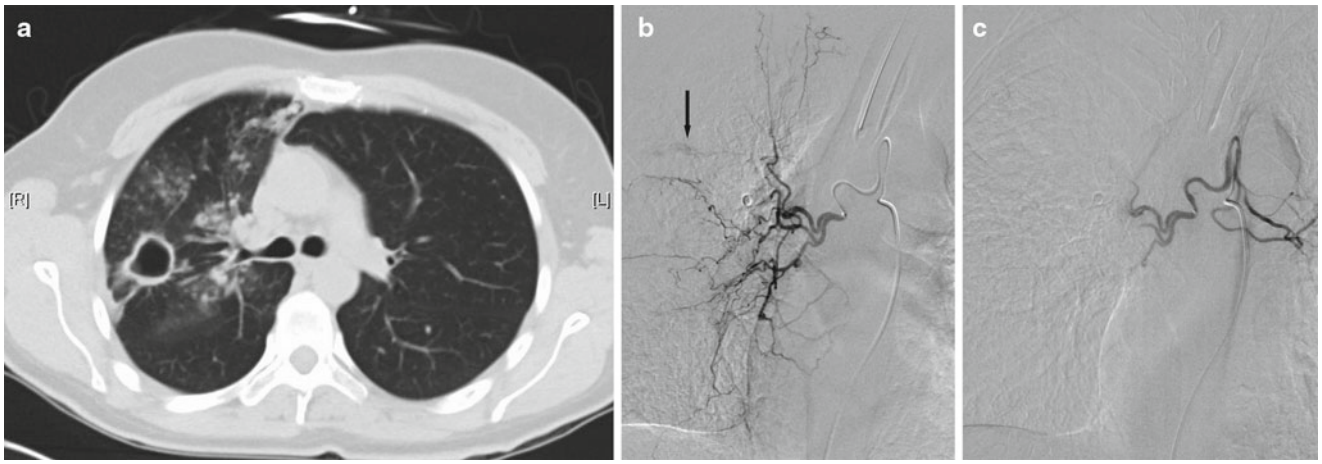

Fig. 44.4 A 46-year-old woman presented with fever, cough, and massive hemoptysis with rapidly progressive hypoxemic failure. The patient required endotracheal intubation, and a bronchoscopy demonstrated a large *right* mainstem bronchus blood clot. The patient stabilized with mechanical ventilatory support and was taken for a chest CT scan which demonstrated a cavitary lesion in the right upper lobe (**a**). She continued to have small amounts of blood from her ETT, and she was taken for BAE. Bronchial artery arteriography failed to demonstrate diffuse bronchial hypertrophy and hypervascularity with a contrast blush in the RUL (**b** – *arrowhead*). Due to the inability to cannulate the suspected culprit vessel, microparticle embolization of the entire artery was performed, resulting in successful BAE and hemoptysis cessation (**c**). Following BAE, the patient was taken to the operating room for rigid bronchoscopy and clot extraction. She was successfully extubated following the procedure (Photos courtesy of S. Trerotola, M.D.)

which will pull the frozen and organized clot out of the airway. The bronchoscopist must be prepared to deal with acute bleeding because clot extraction, while necessary in refractory hypoxemic respiratory failure, can relieve hemostasis with bleeding recurrence.

Definitive Treatment

Bronchial artery embolization (BAE) which was first performed in the 1970s has become the most utilized nonsurgical treatment modality due to its effectiveness both on a short- (over 90%) and long-term (over 80%) basis. It should be considered in patients after initial stabilization and/or after endoscopic treatments are either not helpful or have failed. Successful embolization depends largely on the ability to delineate the vascular anatomy angiographically (Fig. 44.4). In patients with recurrent bleeding despite embolization (10–20% over 6–12 months), repeat embolization can be attempted. Late rebleeding (past 1 year) is usually due to neovascularization or recanalization. BAE complications are uncommon in experienced hands, but bronchial wall necrosis and ischemic myelopathy from inadvertent spinal artery embolization can occur.

Patients with lateralized, uncontrolled bleeding should be assessed early for possible surgery in case they prove to be refractory to temporizing measures or BAE. Need for surgical intervention is rare and usually the treatment choice in massive hemoptysis cases due to leaking aortic aneurysms, hydatid cysts, iatrogenic pulmonary vascular ruptures, and chest trauma. It is contraindicated in carcinomatous invasion of the trachea, mediastinum, heart, and great vessels and in advanced lung fibrosis. The surgical mortality rate in massive hemoptysis (defined as death within 7 days postoperatively) ranges from 1% to 50%, with emergent cases having the highest mortality rate. Common surgical complications include empyema, bronchopleural fistula, postoperative pulmonary hemorrhage, prolonged respiratory failure, wound infection, and hemothorax. Recently, some centers have demonstrated a mortality reduction by avoiding surgical intervention within 48 h from hemoptysis onset if bleeding can be temporized with less-invasive measures.

When massive hemoptysis and/or hypoxemic respiratory failure occurs as a result of nonstructural etiologies (e.g., pulmonary edema, DAH), adequate oxygenation with mechanical ventilator support and other adjunctive measures should be ensured while treatment of the underlying medical condition is initiated. In the setting of suspected DAH, pulse steroids at 1,000 mg Solu-medrol for 3 days followed by 1 mg/kg thereafter with cyclophosphamide 1–2 mg/kg daily should not be delayed. In addition, if Goodpasture syndrome is suspected, plasmapheresis should be instituted while serologic data is pending.

Summary

Massive hemoptysis is an uncommon complication of a variety of systemic and pulmonary diseases. Early measures to protect the unaffected lung (when a unilateral source can be identified) as well as temporizing measures to achieve hemostasis should

be considered while more definitive treatment with BAE or surgical intervention is evaluated. Expeditious and aggressive multidisciplinary management of these patients often can control bleeding and lead to optimal patient outcomes.

Suggested Reading

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Management of Posttransplant Disorders

45

Michael S. Machuzak

Introduction

Airway complications (AC) have been a significant and persistent source of morbidity and mortality since the first human lung transplant took place in 1963. The early incidence ranged from 60% to 80% but has improved to approximately 15% with a related mortality rate of 2–3%. This improvement has played a vital role in the enhanced survival of lung transplant patients. Despite an improvement in overall survival, the prevalence of airway complications has not changed over the past decade. Airway complications are varied in presentation and treatment and seen primarily at the site of the anastomosis but are also found both proximal and distal to the suture line. Complications seen directly at the anastomosis include stricture/stenosis, hypertrophic granulation tissue, necrosis, dehiscence, loose sutures, fistula formation, and infection. Complications seen in proximity to the anastomosis include necrosis, malacia, and distal stricture. Notwithstanding the morbidity related to AC, quality of life is markedly impacted, sometimes negating the benefit of lung transplantation.

Incidence and Prevalence

The reported rate of anastomotic complications ranges from 1.6% to 33% in the literature although most agree with a rate of approximately 15%. Airway complications typically occur within 2 years posttransplant with almost half identified prior to hospital discharge. One of the reasons for the wide variability of prevalence is the lack of a standardized definition of an anastomotic complication. Airway complication rates are lower in heart-lung recipients compared to single or bilateral sequential lung transplants. In centers with experience in bronchial artery revascularization (BAR), the rates may be even lower perhaps related to reestablishment of the bronchial blood supply. Figure 45.1a, b show healthy right and left anastomoses, respectively.

Anatomy

While normally there is a dual blood supply from the bronchial and the pulmonary arteries, the bronchial circulation is not reestablished in standard lung transplantation. Previous anatomic studies have defined fairly consistent origins of the bronchial arteries from the intercostal arteries and descending thoracic aorta. The bronchial circulation provides an important blood supply to the major airways and supporting structures of the lungs. The bronchial arteries arise from the aorta or the intercostals and travel through the hila where small arterials penetrate the muscular layer of the airway and terminate in the bronchial mucosa. This termination is in the form of a submucosal plexus which eventually results in a collateral circulation between the pulmonary and bronchial circulations. Each proximal main stem bronchus receives its primary blood supply from the bronchial circulation although the pulmonary circulation can contribute via retrograde collaterals. While the much larger pulmonary circulation is reestablished at transplantation, the bronchial circulation is not. Therefore, bronchial viability and anastomotic healing are dependent upon retrograde blood flow from the pulmonary to bronchial circulation leaving the anastomosis and distal airway in jeopardy. Coronary collateral blood supply arises at atrial branches from the left and right coronaries. This collateral supplies the main carina as well as the proximal left and right main stem bronchi explaining why the more proximal airways do not seem to suffer the same ischemic risk.

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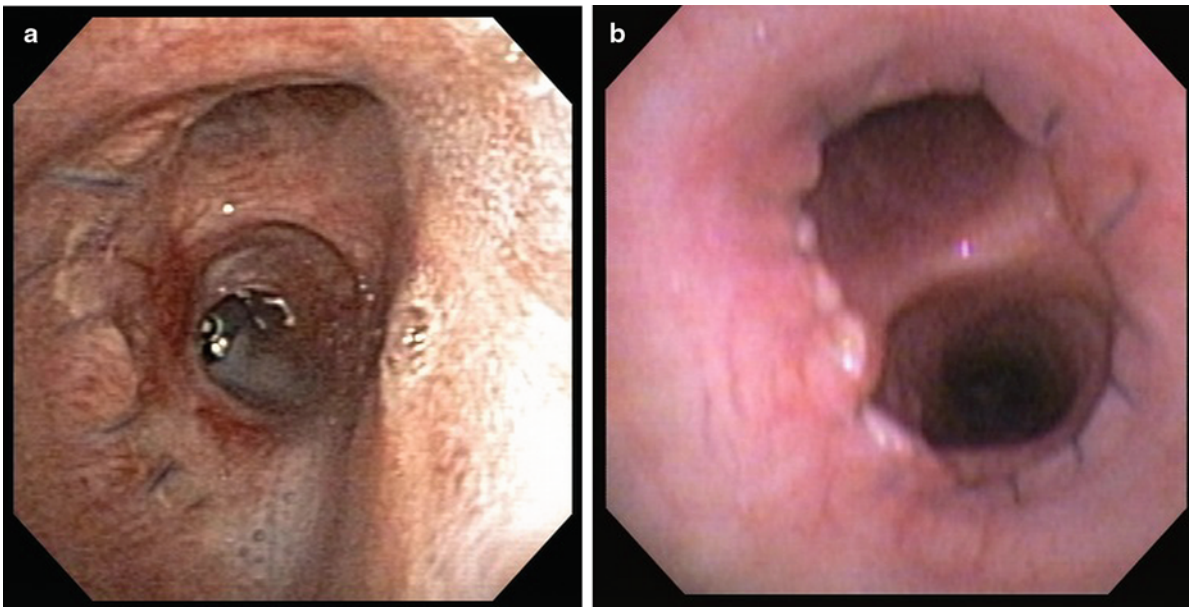

Fig. 45.1 (**a**) Example of a healthy right anastomosis. (**b**) Image 1.1b shows a healthy left anastomosis

Risk Factors

The etiology of airway complications is likely multifactorial. Most theories attribute AC to ischemia, infection, or a combination of the two.

Anastomotic Ischemia

Airway complications have long been attributed primarily to ischemia of the donor bronchus in the immediate transplant period. The native lung blood supply is dual with a component coming both from the bronchial and pulmonary systems. In the standard transplantation surgery, the bronchial arteries are severed and not reanastomosed due to their small size. Collaterals take up to 4 weeks to develop, during which time the donor bronchus is completely dependent upon the retrograde flow from the pulmonary artery. Unfortunately, this is a low-flow, low-pressure system that is poorly oxygenated. This is believed to be a major factor that predisposes the donor bronchus to ischemia leading to necrosis, sloughing, infection, dehiscence, and/or stricture. There are additional factors in the postoperative course which may also play a role. Complications such as hypotension, low cardiac output, corticosteroids, glucose levels, poor tissue perfusion, volume status (overload or dehydration), circulating antibodies, and cytokines among others can affect tissue oxygenation at the cellular level.

Donor Bronchus Length

Closely relating to ischemia is the length of the donor bronchus. A donor bronchus with excessive length is likely more susceptible to ischemia due to the lack of collateral flow in the initial posttransplant period. Therefore, a longer bronchus has less blood flow at the anastomosis. For this reason, the donor bronchus should be shortened with the anastomosis being as close as possible to the secondary carina. Although beneficial from an ischemia standpoint, an anastomosis that is in close proximity to the secondary carina may make the management of a complication more difficult. This is particularly true in the case of stenting as there may not be adequate length to seat the distal end of the stent.

Anastomotic Techniques

Every attempt is made to preserve undisturbed peribronchial tissue in an attempt to maintain the microvasculature. The benefits of particular anastomotic techniques are debated among surgeons, and there is no consensus practice. Wrapping the bronchial anastomosis with omentum or another vascularized pedicle has demonstrated reestablishment of collateral circulation at the level of the donor bronchus. Bronchial omentopexy appeared to be important in the early success reported by the Toronto group. The improvement in early neovascularity in addition to

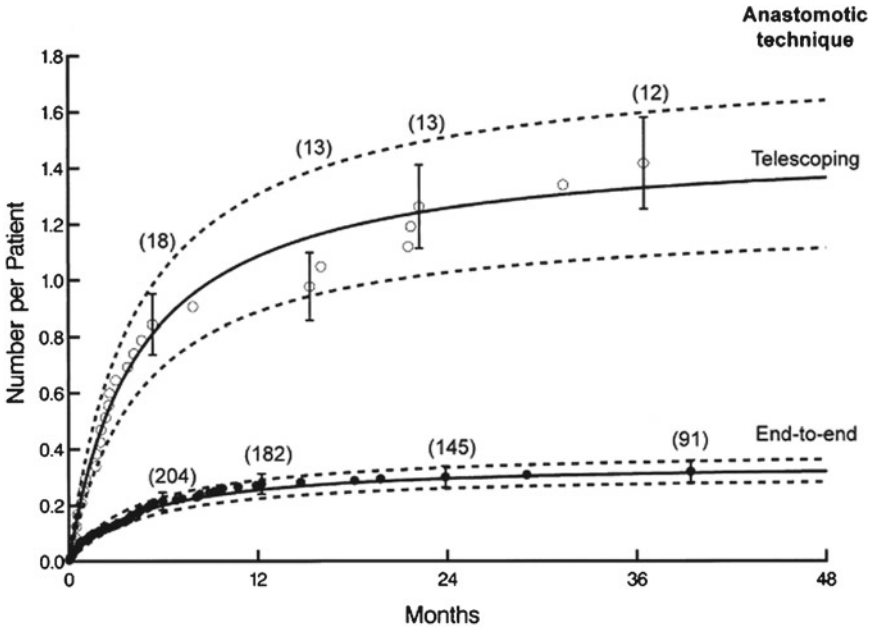

Fig. 45.2 *Anastomotic techniques.* Shows the impact of airway complications (AC) based on type of anastomosis. The rate of AC increases with a telescoping anastomosis. (Reprinted with permission from Mehta AC, et al. Impact of Anastomotic Airway Complications After Lung Transplantation. Ann Thorac Surg. 2007;84:401–409, Graph 4.)

separating the bronchus from the mediastinum and pulmonary artery was an attempt to minimize the effect if a dehiscence were to occur. This procedure added complexity and morbidity primarily due to the addition of a laparotomy as well as a diaphragmatic defect. For these reasons, omentopexy is rarely practiced now. Additional anastomotic coverage with peribronchial tissue or other vascularized flaps have also been described although the data is weak as to their benefit. Anastomotic technique varies by institution and surgeon. There is some data to suggest that the risk of airway complication may be related to the type of anastomosis (see Fig. 45.2). The two most common types of anastomosis are the telescoping technique and the end-to-end anastomosis. Data exists which suggests that the telescoping technique is associated with more complications, particularly obstruction. Despite this, some surgeons still perform a telescoping anastomosis but agree that an exaggerated intussusception should be avoided whenever possible. An intussuscepted airway will predispose to an obstruction simply due to its anatomy. An obstruction seen in this airway will also be more difficult to dilate. In addition to this potential mechanical obstruction, any additional amount of sloughed necrotic tissue will lead to earlier obstructive symptoms. A significant intussusception may also allow for entrapment of the microorganisms between bronchi due to the microbiologic environment. For these reasons, most centers have adopted an end-to-end anastomotic technique as the procedure of choice unless donor-recipient bronchial size mismatch exists.

Donor/Recipient Size Mismatch

Airway complications also appear to be related to donor and recipient size mismatching. Differing diameters of donor and recipient bronchi have traditionally been treated with a telescoped anastomosis. This telescoping may lead to unwanted and potential deleterious stress at the suture line. Almost always, the size mismatch is a donor airway that is smaller than the recipient. A technique to manage this size mismatch is to perform an upper lobectomy on the recipient and anastomose the donor main stem to the bronchus intermedius on the right or the left lower lobe airway on the left.

Miscellaneous Factors

Several other unavoidable risk factors which predispose a lung transplant anastomosis to complications exist. Although many of these risk factors may appear to be logical, most have not been demonstrated across institutions or in multi-institutional studies. Factors such as a male donor and a tall donor have been suggested. The anastomosis is seldom tension-free due to the wall stress created by positive pressure ventilation. This stress may predispose to injury and/or dehiscence. The length of donor time on mechanical ventilation has also been suggested with a time of 50–70 h increasing the probability of an airway complication. This may be related to an increased risk of infection while intubated. Airway anastomoses are sutured in the setting of a contaminated field. The necrosis

often seen also provides a nidus for microbiologic growth. This milieu in conjunction with a suppressed immune system makes infection a major concern.

Immunosuppression/Medications

Although there have been considerable improvements in lung transplant survival, there is still a lag behind other solid organ transplants. Lung transplant patients are maintained at higher levels of immune suppression, but despite this, both acute and chronic rejection remain difficult problems to control, and chronic rejection manifested as bronchiolitis obliterans syndrome (BOS) occurs earlier with more dire consequences than other solid organ transplants. Immunosuppression is critical for the survival of an allograft; however, this may predispose to airway complications due to increased susceptibility to infection and diminished healing. Most immunosuppressive regimens consist of a calcineurin inhibitor (typically tacrolimus) in conjunction with an antilymphocyte (mycophenolate mofetil or azathioprine) and corticosteroid. Deserving special mention is sirolimus (rapamycin, Rapamune) which is a novel macrolide originally developed as an antifungal agent. It was later discovered to have potent immunosuppressive and antiproliferative properties which led to its use in renal and later lung transplantation. While the major drawback of calcineurin inhibitors is renal toxicity, this is seen at a much lower incidence with sirolimus. Sirolimus has been shown to be effective in controlling acute rejection and does not have overlapping toxicities with other immunosuppressants without the associated renal toxicities. This combination would make sirolimus appealing as an adjunctive medicine for the lung transplant population. However, in de novo recipients, sirolimus was shown to dramatically increase the rate of catastrophic airway complications. In particular, the rate of dehiscence was found to be unacceptably high in the early transplant period. The current recommendation is avoidance of sirolimus for at least 90 days after transplantation.

Description and Management of Airway Complications

Comparison of airway complications after lung transplantation is made difficult by the lack of universally accepted classification system. However, there are several classification systems which address airway complications which are utilized. (Table 45.1)

Airway complications can be considered temporally, by etiology or descriptively. Several of the more common descriptive classifications include necrosis, dehiscence, stenosis/stricture, granulation tissue, infection, or fistula. Complications can be categorized as partial or full-thickness necrosis, obstruction, infection, or fistula. Airway necrosis, though not always considered a complication, may cause obstructive symptoms and is the early range of the spectrum including bronchial dehiscence. Obstruction may include airway stenosis from stricture, granulation tissue, or malacia. Included in obstruction is stricture at the anastomosis as well as a non-anastomotic narrowing in segmental or subsegmental airways.

Table 45.1 Classification of airway complications

Classification of airway complications	
Stenosis/stricture	*Anastomotic bronchial stenosis*
	Stenosis <50% of bronchial diameter
	Stenosis >50% of bronchial diameter
	Non-anastomotic bronchial stenosis
	Stenosis <50% of bronchial diameter
	Stenosis >50% of bronchial diameter
Necrosis and dehiscence	*Grade I*
	No slough or necrosis
	Well-healed anastomosis
	Grade II
	Any necrotic mucosal slough observed but no bronchial wall necrosis
	Grade III
	Bronchial wall necrosis within 2 cm of anastomosis
	Grade IV
	Extensive bronchial wall necrosis extending >2 cm from anastomosis
Exophytic granulation tissue	Obstructing <50% of the bronchial lumen
	Obstructing >50% of the bronchial lumen
Malacia	Diffuse tracheal/bronchial
	Anastomotic location
Fistula	Bronchomediastinal fistula
	Bronchopleural fistula
	Bronchovascular fistula
Infectious	*Anastomotic infections*
	Bacterial
	Fungal
	Non-anastomotic infections
	Bacterial
	Fungal
	Viral

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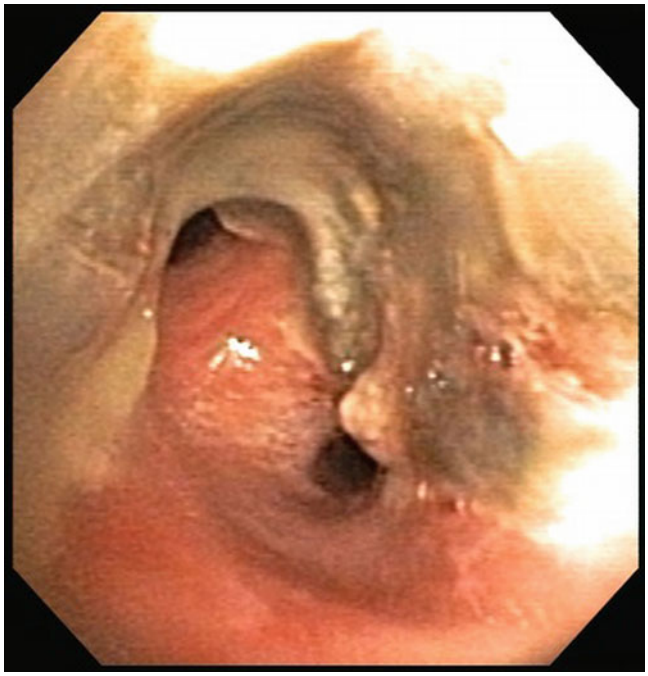

Fig. 45.3 *Necrosis image*. Necrosis in the immediate transplant period. This is a typical sloughing mucosa seen in the first few weeks after a lung transplant. This is the RUL and RBI seen with necrotic mucosa at 3 weeks posttransplant.This necrosis led a significant stricture, seen below

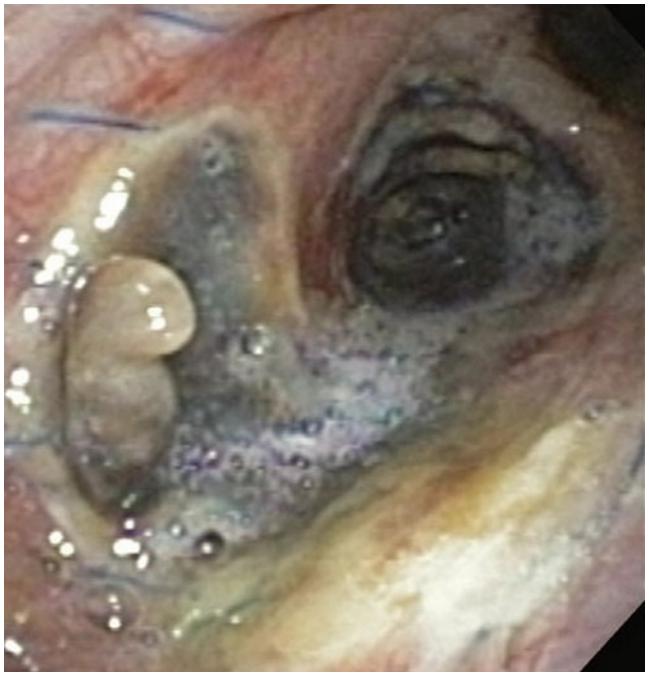

Fig. 45.4 *Dehiscence*. A dehiscence is seen along the medial and posterior wall 2 weeks after transplantation. The dehiscence is seen in the right main stem bronchus. This was successfully managed with a SEMS

Necrosis

Necrosis is seen at many surveillance bronchoscopies but is not necessarily considered a complication. The incidence of necrosis is unknown as because it is not typically reported. An eschar is frequently seen at the anastomosis as well as in segmental bronchi. Necrosis is usually thought of as part of the healing phase as the airway sloughs the ischemic tissue and is subsequently replaced with healthy mucosa as revascularization occurs (Fig. 45.3). Necrosis is seen early in the healing phase but usually will improve within the first few weeks. An ischemic airway with necrosis may eventually lead to dehiscence.

Airway Dehiscence

Airway dehiscence can be a catastrophic complication, especially in the immediate postoperative period. This is typically thought of on a continuum with necrosis. The inciting event is typically ischemia, though infectious complications may be responsible. These problems are difficult to treat and lead to significant morbidity and mortality (Fig. 45.4). Dehiscence can arise despite meticulous suturing technique, wrapping of the anastomosis, and in the setting of a previously uneventful postoperative course.

A dehiscence must be considered when forming a differential diagnosis in any lung transplant patient having a difficult course, especially in one with a prolonged pneumothorax or pneumomediastinum. It can be difficult to diagnose as many of the signs or symptoms which may point toward a dehiscence are those that are commonly seen in the posttransplant period. A chest roentgenogram may intimate dehiscence by pneumomediastinum or pneumothorax while a chest CT has a higher degree of sensitivity and specificity. A CT scan may show dehiscence as evidenced by peribronchial air. The gold standard for diagnosis is bronchoscopy. In the setting of severe necrosis, it may be difficult to see the actual site of dehiscence; however, there are several clues seen endoscopically. Significant necrosis and loose sutures can be a clue that the anastomosis is at risk. Figure 45.5 shows an example of necrosis and loose sutures in an airway which eventually dehisced. Ischemia of the bronchial wall, tension at the anastomosis, positive pressure ventilation, and infection are all considered to be risk factors for dehiscence. Four grades of dehiscence have been described and are included in Table 45.1.

Management of dehiscence depends on the severity. Grade 1 and 2 bronchial dehiscence requires no intervention

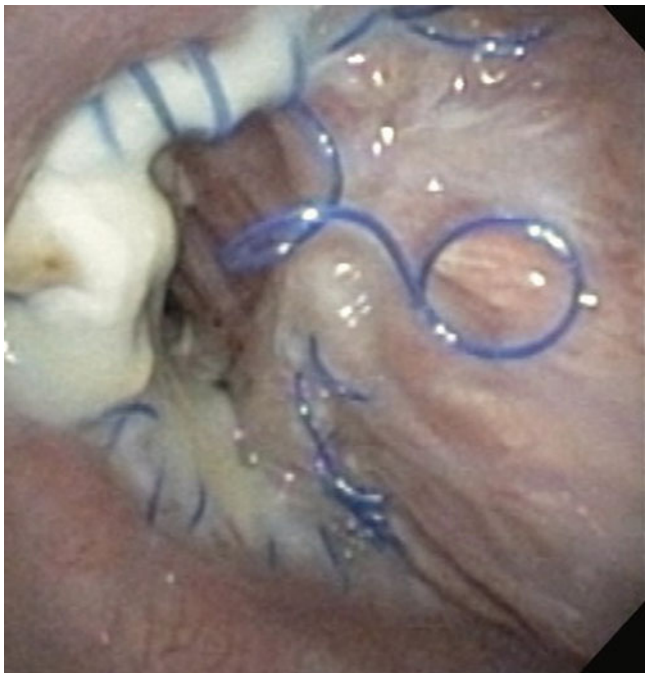

Fig. 45.5 *Loose sutures necrosis.* This is an example of loose sutures and necrosis in an airway which eventually dehisced

except close monitoring. Grade 3 and 4 bronchial dehiscence can be devastating complications. Dehiscence has been managed successfully surgically; however, this is fraught with many complications and a high mortality, primarily owing to the critical respiratory condition of the patient at the time of surgery. Cyanoacrylate glue has been successfully used to close a dehiscence, although this technique will not be successful most of the time. A more conventional approach has been described using uncovered self-expandable metallic stents (SEMS). In this technique, granulation tissue, one of the commonly described complications caused by self-expanding metal stents, is used as a benefit. After the airway patency is optimized with gentle dilation and/or debulking, a non-covered self-expandable metallic stent (SEMS) is deployed across the dehiscence and closely followed. As soon as epithelialization/granulation tissue develops, typically within 1–3 weeks, the stent is removed and replaced until the visible defect is closed. Several cycles of this technique have been shown to allow the bronchial wall to heal. An example of this technique is shown in Fig. 45.6a–e. This technique requires expertise in placing and more importantly in removing SEMS as overly aggressive removal may worsen the injury, often with catastrophic consequences. Bronchial dehiscence, even after successful management allowing for closure, may leave behind other complications such as stenosis, bronchomalacia, exophytic granulation tissue, or fistula formation.

Granulation Tissue

Exophytic granulation tissue may be seen as a result of an exaggerated immune response, similar to a keloid reaction. This is likely related to an exuberant healing response leading to an influx of inflammatory mediators and immune cells. A reaction to loose sutures in the airway or an infection may also be responsible (Fig. 45.7). This is a response seen at the anastomotic site, typically within several months. The major complication tends to be obstructive symptoms, either relating to decreased airflow or mucus clearance. Cough, dyspnea, or a drop in airflows measured by spirometry may be the first clues and should be confirmed bronchoscopically.

Granulation tissue can be a recurrent and challenging dilemma but often responds to mechanical debulking with forceps (rigid or flexible) and in many cases will not return. Other physical debulking modalities may be used such as the bevel of a rigid scope or a microdebrider, in the hands of an experienced operator, as further complications such as bronchial injury may occur. In some cases, a thermal ablative modality may be required. Cryotherapy may be preferred by many since heat energy may lead to further airway injury. The effect of cryotherapy is through cell lysis due to crystallization at the cellular level. This crystallization leads to microthrombi formation. This effect is achieved by bringing the tissue temperatures to −20°C or lower. Effective cryotherapy depends upon the tissue's water content. Granulation tissue is quite vascular and so is ideal for cryotherapy debulking. Bland scar tissue and cartilage are relatively cryoresistant. Advantages of cryotherapy versus other thermal ablative techniques lie primarily in its safety. Cryotherapy does not have the same risks of electrocautery, argon ablation, or laser photoresection. It may also be used safely in the setting of high concentrations of oxygen. A repeat bronchoscopy for removal of sloughed tissue may be required.

Argon plasma coagulation, laser photo resection, and endobronchial electrocautery have also been used for debulking of granulation tissue. Although affective at tissue debulking, airway fires, perforation, gas embolism, and bronchoscopic damage have all been described while using heat-derived techniques. Additionally, there is concern that the heat energy may lead to increased scar tissue formation.

Mitomycin-C may be used in an attempt to minimize granulation formation. Mitomycin-C is an antineoplastic agent which may be used to inhibit fibroblast proliferation. The dose of mitomycin-C varies but typically is in the range of 0.5–1 mg per mL. The mitomycin is applied via pledget, and the area is swabbed with a dwell time of 2–5 min for each application. There are reports of more extreme interventions such as high-dose rate (HDR) brachytherapy and photodynamic therapy (PDT) in the most recalcitrant cases. Although sometimes effective, they are not commonly used modalities. PDT and HDR brachytherapy have been used for

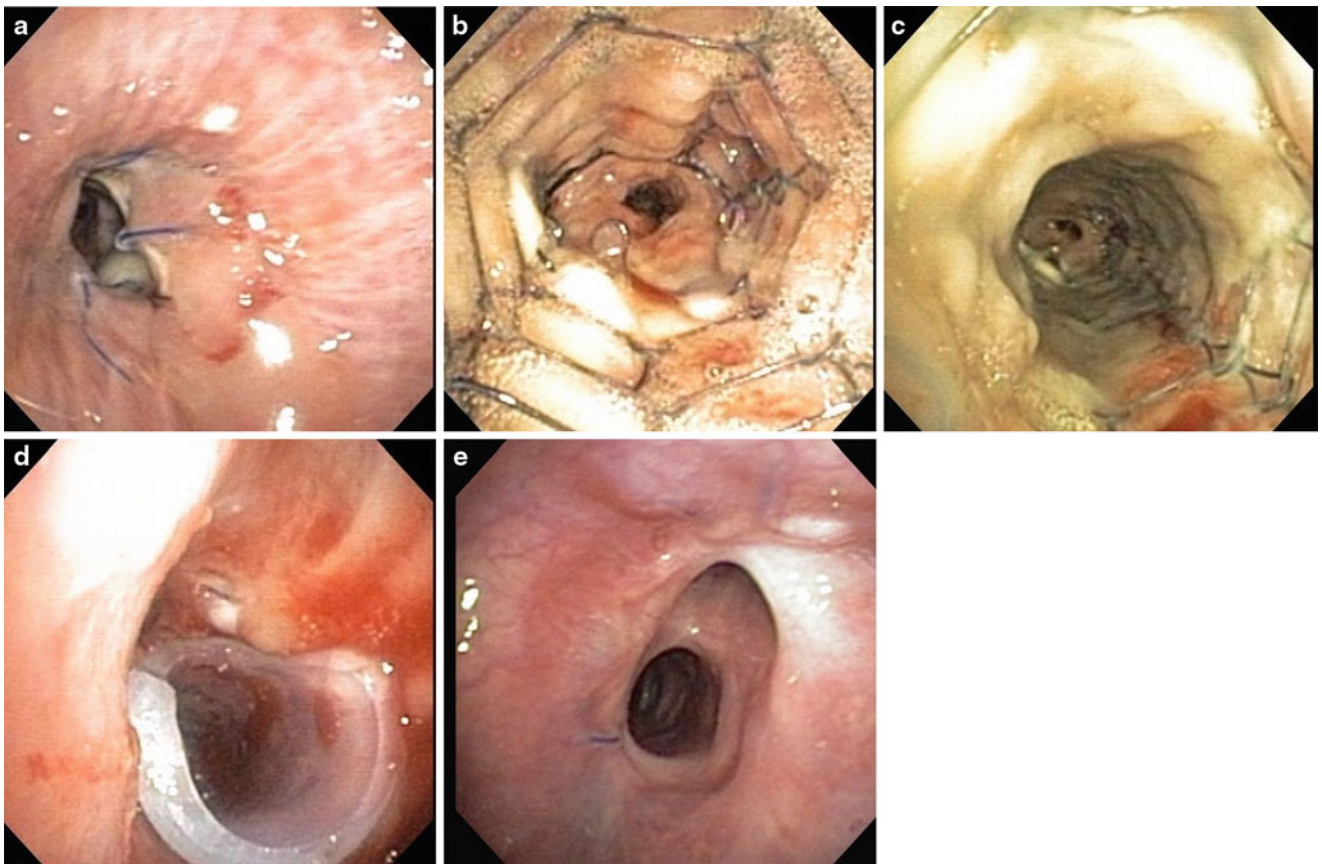

Fig. 45.6 (**a**) *Dehiscence*. The *arrow* pointing to the opening seen is actually a full-thickness dehiscence into the mediastinum. The RBI and RUL were completely occluded by the medial wall. This was treated with SEMS placement and removal × 2 followed by a silicone stent with excellent results, both in appearance and clinical outcome. (**b**) Placement of a SEMS across the area of dehiscence. This will allow for granulation tissue to develop and initiate the healing process. The non-covered stent was chosen both for its increased ability for inducing granulation tissue and to allow for drainage of the right upper lobe (RUL) as the stent "jails" the orifice. (**c**) Two weeks after placement of the SEMS, there is granulation forming along the stent. Once the granulation forms, the stent should be removed and replaced. (**d**) After placement and removal of a SEMS and silicone, stent was required for both stricture and a component of malacia. The silicone stent was also customized by "notching" an area to allow for RUL drainage. The *arrow* is pointing to the RUL. (**e**) The airway has healed, and the patient has a normal level of functioning

both stricture as well as granulation tissue. Both therapies have been associated with serious complications. PDT often requires therapeutic "cleanup" bronchoscopies in order to remove the sloughed mucosa. Hypersensitivity reactions, photosensitivity, cough, and other complications are seen in PDT. HDR brachytherapy has been reported to cause erosion and massive, even fatal, hemoptysis. For these reasons, extreme caution should be used if considering either modality.

Stricture/Stenosis

Bronchial stenosis or stricture is the most common airway complication requiring intervention seen in the lung transplant patient. A bronchial stenosis is most typically seen in an airway that had previously suffered from significant necrosis, dehiscence, infection, or a recalcitrant exophytic granulation tissue which required multiple endoscopic procedures (Fig. 45.8a, b). However, a stricture may develop in a previously normal airway (Fig. 45.8c). Reported incidence ranges from 1.6% to 32%. Stenosis can be seen at the site of the anastomosis, just distal to the anastomosis or in the segmental and subsegmental bronchi. The syndrome of the vanishing bronchus (non-anastomotic stricture) has been previously reported and, like any stricture, can be challenging (Fig. 45.9). The stenosis may extend into the bronchus intermedius, right middle lobe, lingula, and either upper or lower lobe bronchi. This complication, if left untreated or unrecognized, may lead to a significant narrowing or even a loss of distal airways. Stenting may be an option for recalcitrant stenosis particularly in the main stem or bronchus

intermedius, but due to anatomic constraints, stenting is not typically done in other segments and close observation with repeated dilations is often required.

Bronchial stenosis is typically managed with mechanical dilation. This can be performed in conjunction with other modalities. The electrocautery blade (knife) or several well-placed laser incisions often precede the dilation of a dense stenosis. This is previously been described and referred to as the "Mercedes Benz" technique. This technique is used to allow for preferential tearing of the scar in the areas previously incised when the dilation occurs. It is common practice, although not routine at all institutions, that a transbronchial needle injection of steroid may precede a dilation and often mitomycin-C is done afterward with particular attention being paid to the areas of mucosal injury. The methods of dilation vary from institution and include the use of a bougie, a rigid bronchoscope or inflatable balloon. Though no method has been shown to be superior, the inflatable balloon has several advantages. Inflatable balloons come in a myriad of sizes which can allow for a gradual and more customized dilation (Fig. 45.10). It is a much quicker and simpler task to merely change to a larger balloon for a more aggressive dilation than to use several rigid bronchoscopes. The rigid bronchoscope technique is valuable in many cases as it allows for direct visualization and tissue debulking during the dilation process. Additionally, once the rigid scope has been advanced past the stricture, the scope may be held in place for a longer period of time while still allowing for ventilation to one or both lungs. A balloon will occlude the airway and prevent ventilation which may be significant in the case of a unilateral transplant. The use of the rigid scope is also necessary if a silicone stent is being placed in the area of stenosis. The rigid dilation technique is quite effective but does have the potential for airway injury if not in experienced hands.

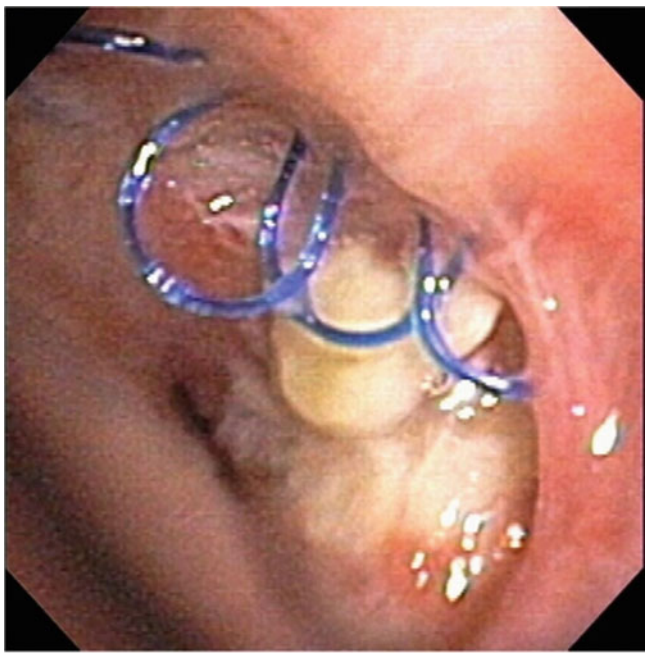

Fig. 45.7 *Exophytic granulation tissue.* This is an example of granulation tissue at the anastomosis. As you can see, there is considerable obstruction of the bronchial lumen. Additionally, there is evidence of loose sutures often seen in the setting of a prior dehiscence (mentioned previously). The dehiscence may well be the inciting factor for the granulation tissue

Stenting is required in cases of particularly recurrent stenosis although in this immunocompromised population, placement of any foreign body must be carefully considered. Silicone stents are the preferred type of stent in any benign stenosis (Fig. 45.11). There are several potential advantages to silicone stents over SEMS. Silicone stents are shown to have a decreased incidence of granulation tissue and are relatively easy to remove even if in place for extended

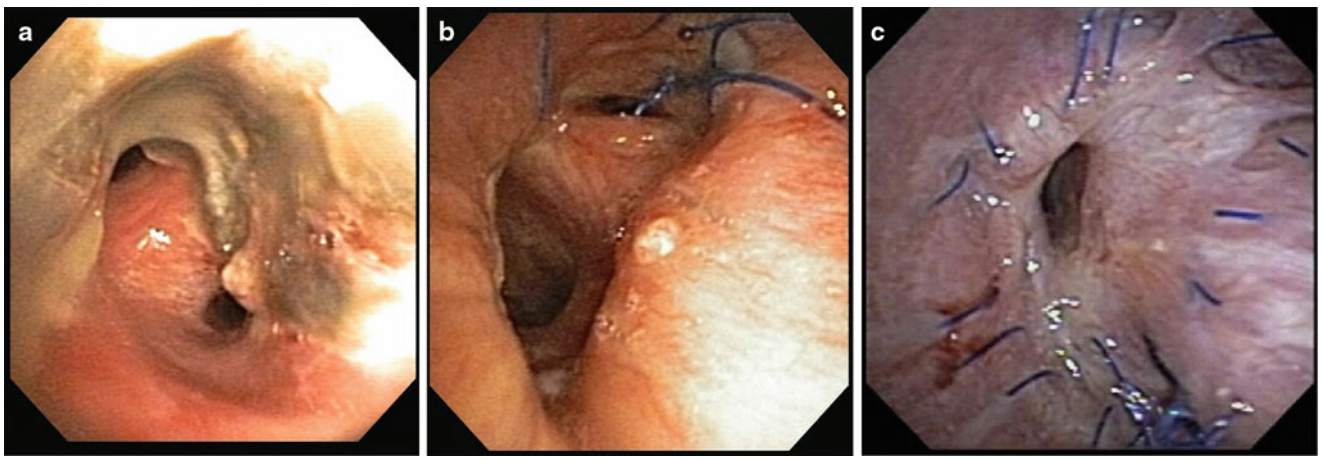

Fig. 45.8 (**a**, **b**) *Stenosis/stricture.* Example of necrosis (**a**) leading to a stricture (**b**) seen at the left main stem anastomosis. (**c**) *Stricture.* This is an example of a dense fibrotic stenosis seen at the anastomosis

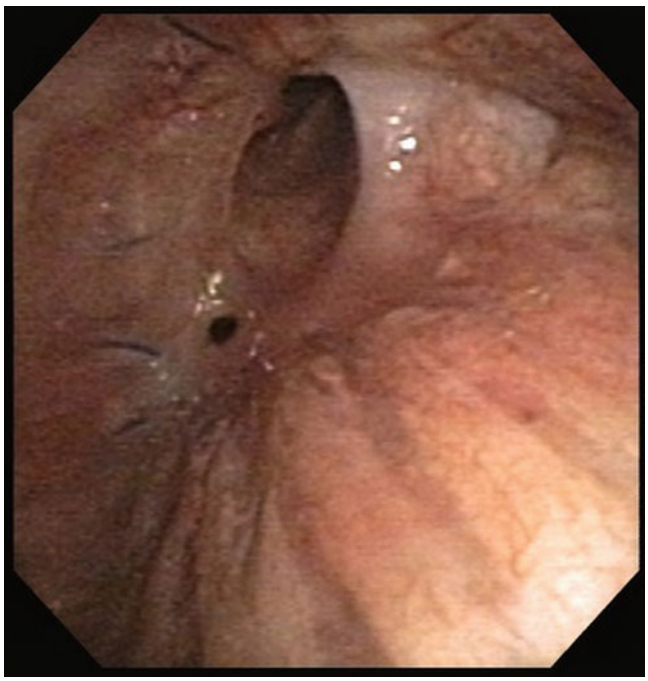

Fig. 45.9 *Non-anastomotic stenosis/stricture*. This is the result of an exuberant healing response after significant necrosis. This is an image of a RUL and RBI seen in a prior example of necrosis (Image 1.2). The RBI is merely a pinhole with <2 mm diameter. This is a classic example of the distal non-anastomotic stricture or vanishing bronchus syndrome. The management of this stricture follows in images 45.9 through 45.12

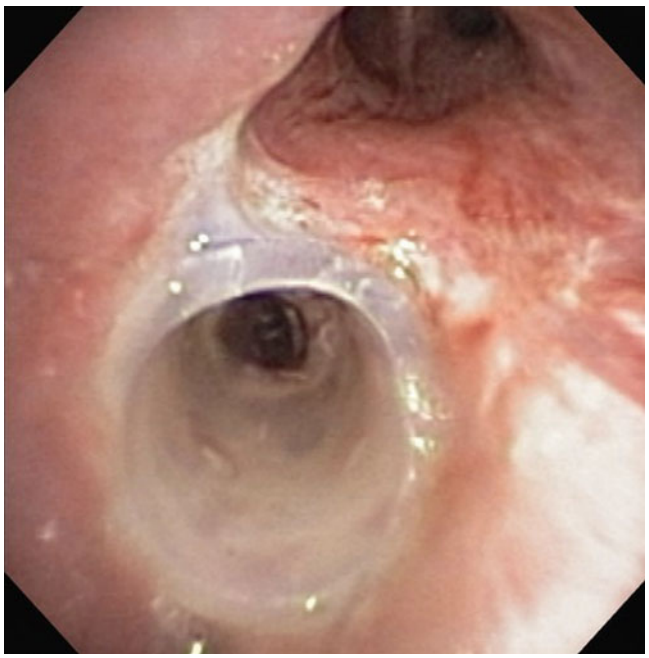

Fig. 45.11 *Silicone stent in a non-anastomotic stricture (VBS).* This is an example of a silicone stent sitting at the RBI just distal to the anastomosis. This stent is well seated and providing mucus clearance and improved airflow in a previously stenotic bronchus

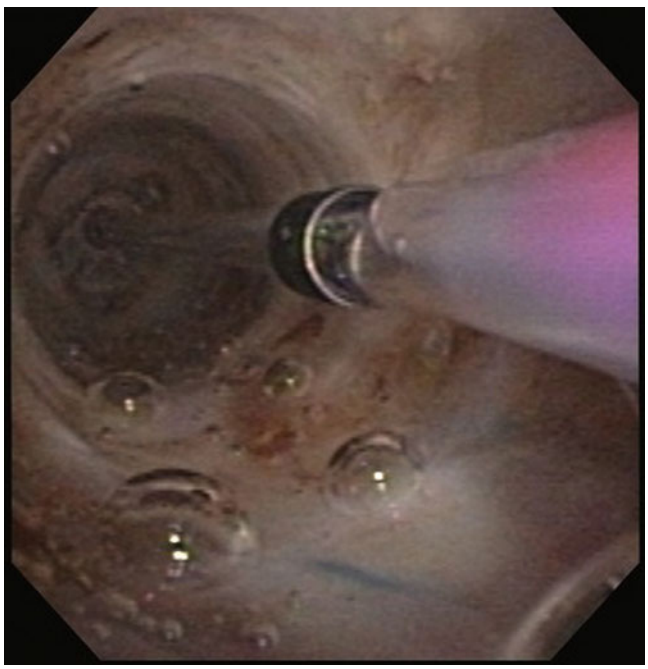

Fig. 45.10 *Balloon dilation*. View through a balloon during the dilation process. This is an example of balloon dilation. The scope is pressed against the balloon to allow for an image of the area being dilated. A *blue* suture (4.0 proline) at the anastomosis is seen at approximately 6 o'clock

periods. Silicone also allows for modification of the stent (Fig. 45.6d). The stent may be custom cut to a specified length or notched to allow for drainage of a lobar bronchus. Silicone stents are not without their associated problems which include increased rates of migration, a lower internal to external ratio, mucus plugging, requirement of rigid bronchoscopy, and chronic halitosis. Complications typically present early, within the first few weeks to a month after placement. The complications in the transplant population are similar to non-transplant patients. Despite the potential complications, excellent results can be achieved (Fig. 45.12).

Self-expandable metallic stents (SEMS) were initially used quite liberally for several reasons. The ease of deployment primarily due to their ability to be deployed via a flexible scope made this option quite popular. SEMS demonstrated other advantages such as their external to internal diameter ratio, decreased migration, superior flexibility, and ability to conform to complex airways. SEMS, if left in place too long, become quite difficult and, in some cases, are impossible to remove, leading to a slippery slope of interventions to control the complications related to stent and not the stenosis. Reports of excessive granulation tissue, mucous plugging, stent fracture, bacterial or fungal colonization, chronic halitosis, and airway and vessel perforation leading to

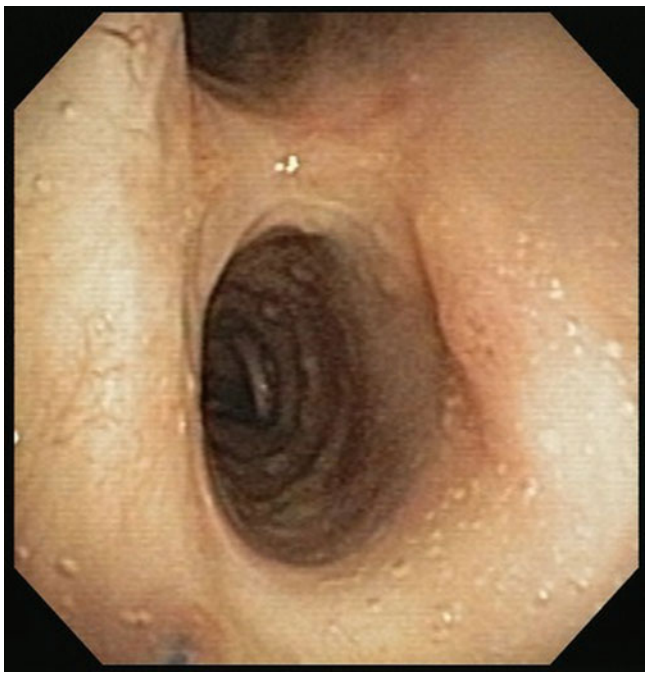

Fig. 45.12 *Stenosis, VBS S/P treatment.* This is the same stenotic airway after balloon dilation and stent placement. After removal of the silicone stent, the RBI remains open

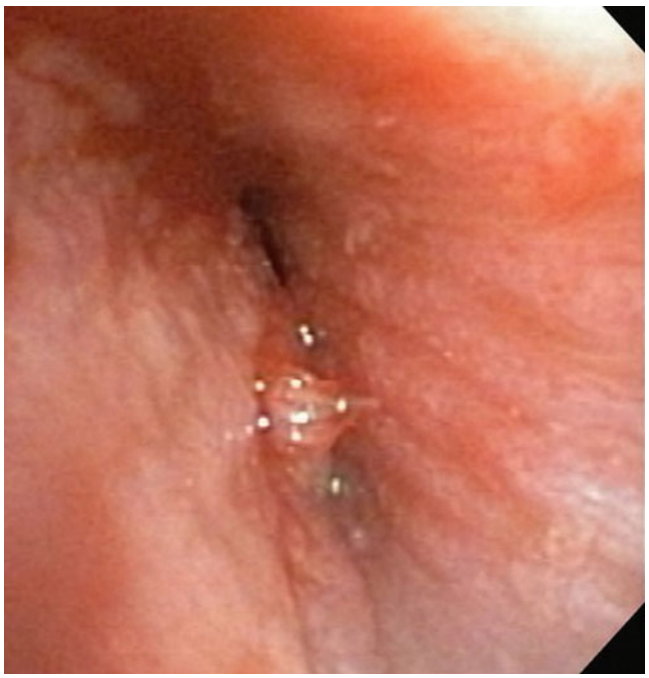

Fig. 45.13 *Malacia.* Bronchial malacia is seen as a collapse of the luminal diameter of >50%. This is an example of a left main stem bronchus with malacia S/P transplant

massive hemoptysis have all been described. These concerns led to an FDA black box warning in benign disease.

If all interventions fail and the patient is an otherwise optimal candidate, then rarely a re-transplantation, sleeve resection, or reconstruction of the anastomosis may be undertaken. A re-transplantation is very rare due to a high surgical risk and less favorable survival. Yearly, only 2% of lung transplant patients are repeat recipients, done primarily for graft failure or BOS.

Malacia

Tracheobronchial malacia is defined as 50% or greater decrease in the diameter of the lumen typically seen on expiration (Fig. 45.13). This loss of diameter may be present due to loss of the cartilaginous support or due to excessive dynamic airway collapse (EDAC) of the posterior wall. Malacia may be seen at the anastomosis, proximal or distal. The etiology is unknown but is possibly related to recurrent injury or ischemia. Malacia may be present, though not recognized, prior to transplant in either the donor or recipient side due to positive pressure ventilation at the time of the perioperative bronchoscopy. The malacia seen in the post-transplant patient usually presents within the first 3–4 months as an intractable cough, wheezing, dyspnea, recurrent infections, or inadequate clearance of secretions. The cough may be the typical "barking" cough often seen in patients with typical malacia. The signs and symptoms are not uncommon to the transplant patient as many of the typical transplant-related pulmonary complications may present identically. A high index of suspicion must be present for all airway complications, including malacia. A dynamic chest CT may suggest this diagnosis, yet despite a high sensitivity, the gold standard remains bronchoscopy. Surveillance bronchoscopy is often performed at discrete intervals according to each program's individual protocol. These bronchoscopies are often the first evidence of malacia. It is important to consider that if bronchoscopies are done under general anesthesia with positive pressure ventilation, the degree of malacia may be underestimated.

Tracheobronchomalacia may be a primary problem relating to the anastomosis or may be a secondary problem due to a physiologic change brought about by an anatomic, distal, or parenchymal problem. Recently, a report of severe scoliosis leading to a diffuse malacia distal to the anastomosis has been reported. It is important to first rule out other etiologies such as infection, acute rejection, and anatomic or associated pleural or chest wall diseases. While malacia at or near the anastomosis is not typically thought of as a major concern, it may require stenting. Stents have been shown to be effective at restoring and maintaining airway patency, allowing for liberation from mechanical ventilation, and improving mucus clearance, allowing for resolution of infection (Fig. 45.14). When stenting is required, it should be with a silicone stent and not a metal stent, unless all other avenues have been

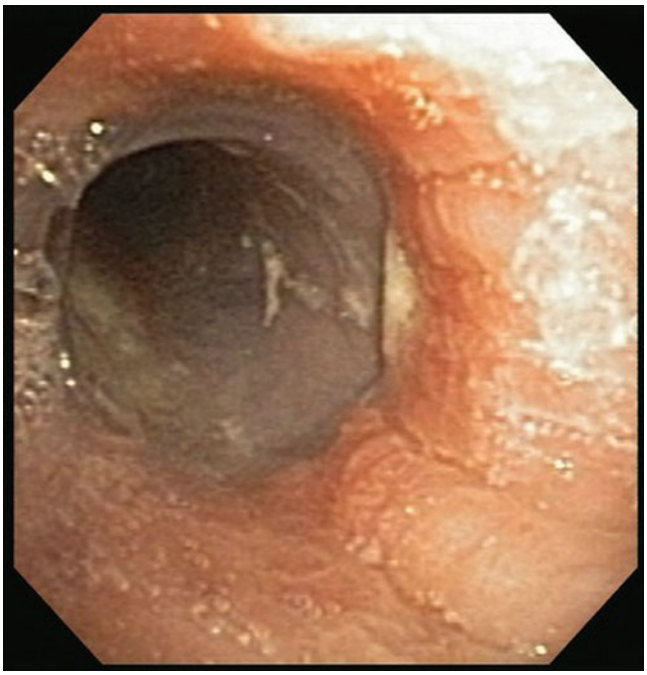

Fig. 45.14 *Stenting malacia.* Image 1.13 shows the same malacic airway S/P stenting

extensively exhausted. Although placement of a silicone stent may be straightforward, it is not uncommon for complications to develop. In some cases, anatomy may not allow for silicone stent placement and may require a SEMS. The usual concerns for placement of a metal stent in benign airway disease apply. Stent placement may provide significant palliation of symptoms with proper patient selection, placement by an experienced endoscopist, and routine follow-up.

Infection

The combination of immunosuppressive drugs, exposure to donor and native airway flora, as well as the external environment make infections inevitable. Another complicating factor is that many transplant patients have already become colonized with organisms, many of which have developed drug resistance. Infectious complications in the transplantation are quite common and involve a wide range of organisms. The ischemia and necrosis in the immediate posttransplant period when immunosuppression is at its highest make the anastomosis quite susceptible to microorganisms. The addition of a post-thoracotomy pain with decreased mucociliary clearance adds to the impairment of the host defense. As previously mentioned, the anastomosis occurs in a contaminated field, and in some cases, the anastomotic technique may predispose to infection. Organisms may become entrapped in the overlapped area of the intussuscepted bronchus increasing infectious risk. The obvious, acute issues of pneumonia, bronchitis, or septicemia must be considered though delayed effects are often seen. Infection may predispose the airway to formation of granulation tissue, stricture, fistulas, or a frank dehiscence. For these reasons, any suspected airway infection should be treated aggressively.

The most frequently acquired infections are bacterial with Pseudomonas and Staphylococcus aureus making up the majority. Saprophytic fungal organisms are also quite common. Aspergillus is of particular concern as it has a strong relationship with subsequent development of airway complications. Cladosporium, Candida, and Scedosporium subspecies have also been described in the literature. Accurate identification of the organism and its susceptibility is critical to any treatment algorithm. Appropriate antibiotics or antifungals are the mainstay of treatment. While the majority of the infections are treated using intravenous or oral antimicrobials, the use of inhaled treatments is often critical for recovery. Periodic bronchoscopic debridement is also useful in removing the nidus for infection. Diagnosis of a true airway infection may be difficult, as the usual signs and symptoms associated with a systemic infection are often absent and distinction between infection and colonization may not be obvious. Some key factors used to distinguish one from the other may include the presence of airway erythema, pseudomembrane formation, or ulceration.

The use of prophylactic antibiotics, antifungals, and routine bronchoscopic surveillance, as well as the increased use of inhaled antibiotics, has all been employed in an attempt to decrease the incidence of this troublesome complication.

Fistula

Bronchomediastinal, bronchopleural, and bronchovascular fistulas are fortunately quite rare but can be devastating complications. Ischemia and/or infection are typically the inciting events. The management of each type of fistula differs slightly, according to their individual anatomy.

A bronchomediastinal fistula will typically present as a mediastinal infection and occasionally bacteremia. The most common location of this fistula as others is at the anastomosis; however, it may occur at any location in the airway.

A bronchopleural fistula will typically present in the early postoperative period. Its presentation is often that of dyspnea and subcutaneous emphysema and may progress to hypotension or a tension pneumothorax. The management may vary depending on the clinical status of the patient, timing, and size of the fistula. A thoracostomy tube is the initial step to allow for evacuation of the air to prevent tension physiology as well as antibiotics to either clear or prevent an empyema which can be a fatal complication. As the complications

involved with a surgical closure are quite high, the initial choice is often endoscopic management. Surgical options include a chronic open drainage such as an empyema tube or in some cases a surgical window. Once the infection is under control, then surgical closure may be attempted. Bronchoscopic closure techniques have been described and include the use of cyanoacrylate glue, fibrinogen plus thrombin, or placement of a bronchial stent. The stent may be silicone or metal though typically a self-expanding metal stent is used in this situation. The individual anatomy will dictate the use of a covered or uncovered stent. As mentioned with the treatment of dehiscence, the granulation initiated by the self-expanding metal stents may allow for closure of the fistula. However, whenever considering placement of a metal stent, it must be remembered that complications for stent placement include erosion and fatal hemoptysis.

Bronchovascular fistula is the most feared complication and is typically fatal. This is typically between the airway and the pulmonary artery anastomosis although they have also been described to the aorta and left atrium. A sentinel bleed is typically followed by massive fatal hemoptysis. Any presentation of more than mild hemoptysis should be investigated with bronchoscopy to inspect the airways and localize the site of bleeding. Surgical is the only possible salvage therapy and likely requires transplant pneumonectomy.

Management Summary

The management of airway complications is frequently complicated. There are many modalities which may be used. The optimal modality is selected based on many criteria individualized to a particular patient problem There is no direct evidence that cryotherapy, laser photoresection, electrocautery, or argon ablation is a superior modality. Dilation of a stenosis using an inflatable balloon, a rigid bronchoscope, or a bougie dilator is dependent upon availability, experience, and preference of the physician. The management should be done in a multidisciplinary approach by an experienced team well versed in all modalities.

Bronchial Artery Revascularization (BAR)

As we have discussed, early morbidity and mortality after lung transplantation is frequently related to anastomotic complications. These complications are typically attributed to ischemia particularly in the first few hours to days after the transplantation, prior to the development of collateral blood flow. Reestablishment of circulation at the airway anastomosis via bronchial artery revascularization has been shown to decrease the rate of anastomotic complications as well as postponing the incidence of bronchiolitis obliterans syndrome. Data presented by the Copenhagen lung transplant group supports this as well as anecdotal evidence at the Cleveland Clinic. Bronchial artery revascularization has also been reported to have superior long-term survival. Re-anastomosis of the bronchial arteries can restore peribronchial tissue oxygenation and improve anastomotic healing after lung transplantation. Bronchial artery revascularization may not be possible in every patient due to anatomical abnormalities or problems with graft harvesting. However, it is a hope of all those involved in this technique that improvement in the peribronchial and anastomotic circulation and microperfusion will lead to a drastic decline in this morbid and challenging complication (Table 45.2).

Table 45.2 Summary of modalities

Dilation
Balloon
Rigid
Ablation
Cautery (probe/knife/blade)
Laser (Nd:YAG or YAP)
Cryotherapy
Microdebrider
Transbronchial steroid injection
Mitomycin-C application
Stent placement
SEMS, hybrid, silicone
High-dose rate (HDR) brachytherapy
Photodynamic therapy (PDT)
Photodynamic Therapy (PDT)
Surgical repair
Anastomotic stricture

Impact of Airway Complications

There is no question that airway complications have a significant impact on the quality of life of the transplantation. Patients who suffer from airway complications must deal with frequent interventions and recurrence of symptoms. Although endobronchial interventions may significantly improve the FEV1 and allow for increased exercise tolerance and a minimization of symptoms, the repeated visits and procedures can be quite burdensome. Keeping in mind that many patients who undergo a transplant do so with the understanding that the survival will not necessarily be increased, but rather they will have an improved quality of life. The frequent procedures and obstructive symptoms no doubt have a detrimental effect on this proposed benefit. The impact on survival may not be as apparent. The overall survival after a lung transplant is approximately 50% at 5 years. Patients with treated

anastomotic airway complications have equivalent early mortality rates to those patients without complications. There does appear to be an increased late risk beginning at approximately 18 months. In patients who received no treatment for their airway complications, there was a higher early mortality, but their late risk was equivalent to patients who had no airway complications.

Conclusion

Complications associated with lung transplant are varied and complex. Multiple management strategies may be employed, but due to the differences in the types of complications, many different techniques are often employed for a successful outcome. Improvement in surgical technique, postprocedure management, immunosuppression, endoscopic techniques, and donor and recipient selection is likely to lead to optimal outcomes. Currently, there are no well-defined, randomized controlled trials which clearly show a superior algorithm of care. In the future, we hope to define the optimal treatment in this heterogeneous and complex patient group. The management of each complication requires an individualized multidisciplinary approach by a team with considerable expertise and experience.

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Foreign Body Removal

46

Mark E. Lund

Introduction

Arguably, the birth of interventional pulmonology was on March 30, 1897. On that day, Gustav Killian first removed a pork bone lodged in the right main bronchus of a living human. Thus, the origin of mitigating aspirated foreign bodies coincides with the inception of interventional pulmonology. Subsequently, Chevalier Jackson brought the technique of rigid peroral bronchoesophagoscopy to the United States. While practicing in Philadelphia, Pennsylvania, he developed instruments and techniques to facilitate airway intervention.

Airway foreign bodies have been managed by multiple disciplines, including pulmonology, otorhinolaryngology, thoracic surgery, and interventional radiology. Chevalier Jackson's influence remains present as both otorhinolaryngologists and interventional pulmonologists lay some birthright claim to Dr. Jackson, and both specialties handle the majority of airway foreign bodies.

Timely diagnosis, driven by a high index of suspicion, and expedited removal improve the clinical outcome. This chapter will review the incidence and risk factors for inhalation of a foreign body. Its primary goal is to define the diagnostic evaluation and therapeutic approaches to removal of airway foreign bodies.

Epidemiology

In 2007, the National Safety Council reported 3,700 choking cases with an estimated 1.2 deaths per 100,000 in the United States. According to the US Centers for Disease Control and Prevention, foreign bodies resulted in an estimated 17,537 emergency room visits for children less than 14 years of age in 2001. Tracheobronchial foreign bodies occur much less frequently in adults with an estimated incidence of 0.66/100,000 in the United States. A retrospective evaluation by Debeljak noted only 0.2% of 37,466 bronchoscopies over 24 years were for foreign body removal.

Aspirated foreign bodies exhibit a bimodal age distribution. It is clear that young children explore the world with their mouths. Hence, it is not unexpected to find that children aged 1–2 are commonly at risk for aspiration of a foreign body. However, the second peak incidence varies significantly. According to the National Safety Council in the United States, the peak incidence of asphyxiating foreign bodies occurs in those younger than 1 year and the elderly aged over 75. In contrast, Hsu and colleagues reported, in a Taiwanese study including 459 airway foreign bodies over 27 years, peak incidences at age 2 and at age 21–30. This variation was thought to be related to alcohol consumption. These facts notwithstanding, age should not remove aspiration from the differential if other factors suggest the possibility.

Anything that impairs deglutition may result in predisposition to aspiration of a foreign body. Old age, impaired level of consciousness (trauma, alcohol intoxication, sedative hypnotic use, or other intoxicants), mental retardation, stroke, neuromuscular disease, Parkinson's disease, dental procedures, tracheal stoma, seizures, and brain tumors are common contributing factors. Iatrogenic increase in the risk of aspiration may occur after general anesthesia or conscious sedation. Interestingly, select populations are at increased risk for aspiration of particular foreign bodies due to cultural practices. For example, there is a noted prevalence of aspirated pins in women from regions that wear head scarves.

Virtually anything that can fit in the oropharyngeal cavity may be aspirated. In adults and children, foodstuff makes up the majority of aspirated material. Common foreign bodies include nuts, particularly peanuts, seeds, bones, and natural and false teeth. In some patient populations, unusual materials may be aspirated. Examples would include pins, stoma caps, and glass from crack pipes (see Table 46.1).

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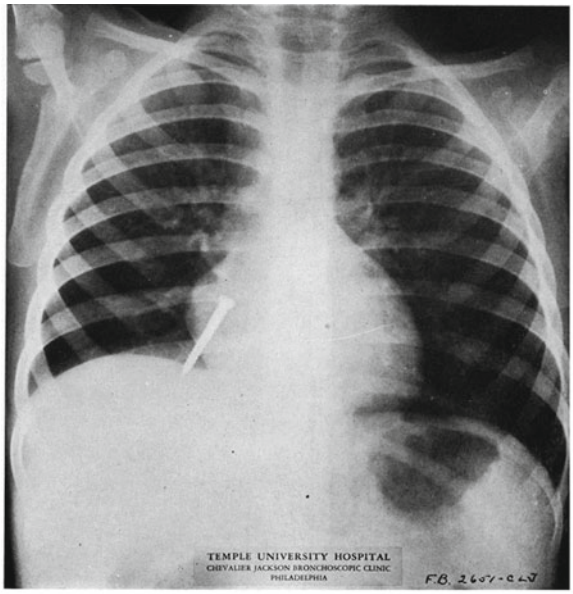
Table 46.1 Types of foreign bodies

Organic	Nuts (peanuts, almonds, walnut, pistachio, etc.)
	Seeds (watermelon, sunflower, chickpea)
	Fruits (apple, tangerine, peach)
	Coffee beans
	Dried cereals
	Popcorn
	Candy
	Rhubarb
	White cedar
Metallic inorganic	Pins
	Hypodermic needles
	Bullet
	Jewelry: earrings
	Dental crowns (Fig. 46.2), implants, bridges
	Coins (Fig. 46.4)
	Knife and razor blades
	Silver Jackson tracheotomy tube
	Nail clippers
	Nails
	Tweezers
Plastic inorganic	Endotracheal tube
	Nasopharyngeal Airway
	Intubating introducer
	Toys and pearls
	Condom
	Stoma button
	Dentures
	Plastic wrap
	Pen cap
	Drug delivery devices (Turbuhaler disc; spray cover)
Mineral	Natural teeth
	Bones (chicken, fish, etc.)
	Stone
	Glass (fragments – Fig. 46.3, cocaine pipe, etc.)
Endogenous	Broncholiths (Fig. 46.5)
Transbronchial erosion	Mediastinal FB: gauze, gauze pledget post-mediastinoscopy
	Rib used for tracheoplasty
	Esophageal stents
	Teflon pledget for reinforcing bronchial stump
Misc	Endoscopic video capsule
	Ascaris lumbricoides
	Shrimp
	Passalid beetle
	Medications: ferrous sulfate, aspirin, kaopectate, cholestyramine, phenobarbital, tetracycline, mineral oil, iron sulfate, fentanyl patch



Photograph Courtesy Temple University Hospital

Fig. 46.1 Chest X-ray obtained for Chevalier L. Jackson, M.D. in the evaluation of a suspected foreign body at his bronchoscopy clinic at Temple University Hospital in the 1930s. (Photograph Courtesy Temple University Hospital)

The type of foreign body will usually influence the local tissue reaction. While inert foreign bodies may have an irritant effect, the overall inflammatory component is limited. There may be direct tissue injury from aspirated sharp objects such as pins, knife blades, razors, glass shards, or nail clippers. Conversely, some objects particularly organic substances, such as nuts, can create an intense inflammatory response. It has been reported that granulation tissue can result within a few hours of contact with the airway wall. Aspiration of various medications, including tetracycline and iron tablets, can also lead to significant inflammatory responses. Expansion of foreign bodies, both organic material and medications, is caused by rehydration. These rehydrated items can become wedged, thus compounding the difficulties of removal, especially when concurrent granulation tissue is present.

Broncholiths are an endogenous foreign body that can erode into the airway. Other eroding foreign bodies are iatrogenic. Examples have included an autologous grafted rib used for tracheoplasty, gauze pledgets, and esophageal stents. With newer technology, capsule endoscopes are a more common cause of iatrogenic foreign bodies. After snare cautery through the stalk of a pedunculated airway mass, distal escape of the excised tumor acts as a foreign body. These freed tumors may oscillate from side to side and occasionally present difficulties if they are calcified or very large.

Because of their shape and aerodynamic qualities, some foreign bodies may lodge very deep. This can be due to initial aspiration or distal migration. Once distal impaction occurs,

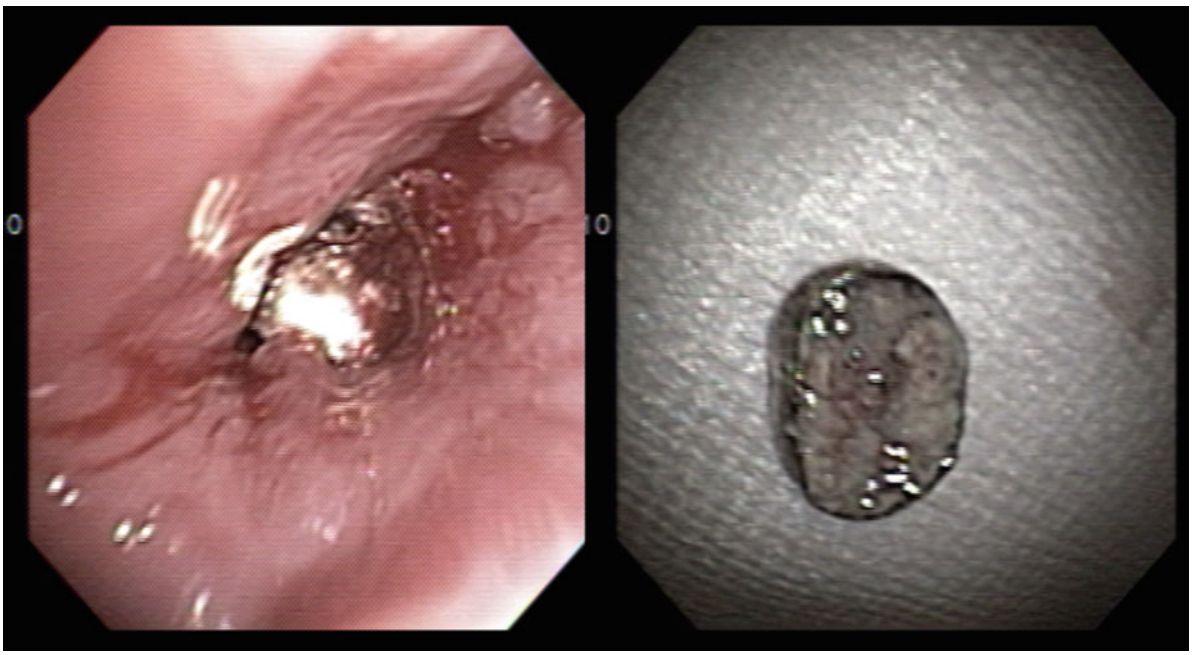


Fig. 46.2 Dental crown impacted in the airway and post removal. (Courtesy H. Colt and S. Murgu, UC Irvine, www.bronchoscopy.org)

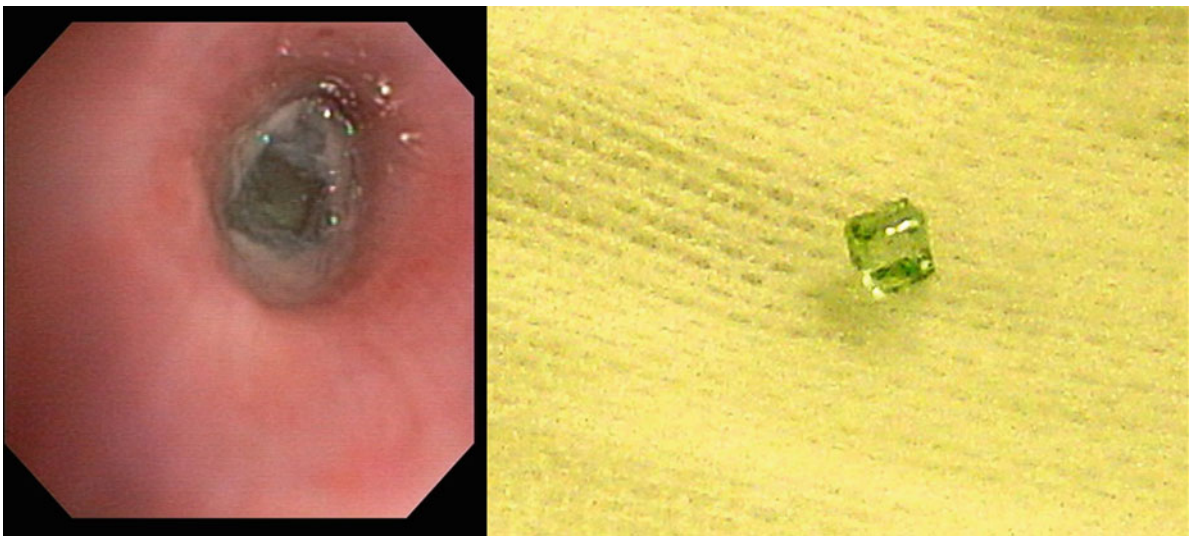


Fig. 46.3 Glass fragment impacted in the airway and post removal. (Courtesy H. Colt and S. Murgu, UC Irvine, www.Bronchoscopy.org)

as in grass inflorescence, the significant inflammatory response may require surgical wedge or lobar resection.

Clinical Presentation

Upon aspiration of a foreign object, patients present with various acuities and wide-ranging symptoms. Acute asphyxic choking with rapid decompensation and death may occur. Basic life support training suggests evaluating the oropharynx for obstructing material in evaluating a patient with cardiopulmonary arrest. Patients experiencing asphyxia will be unable to talk, usually be unable to cough, and commonly exhibit the universal choking sign of having their hands around their throat. Significant symptoms may also occur in acute non-asphyxic aspiration. If a foreign body is subglottic but extrathoracic, inspiratory stridor may result. Acute dyspnea and the sudden onset of wheezing may also occur with high-grade narrowing of either tracheal or main bronchial lumens. Although these symptoms may persist in many patients, the acute episode is often followed by a rather asymptomatic period. This period may be marked with an

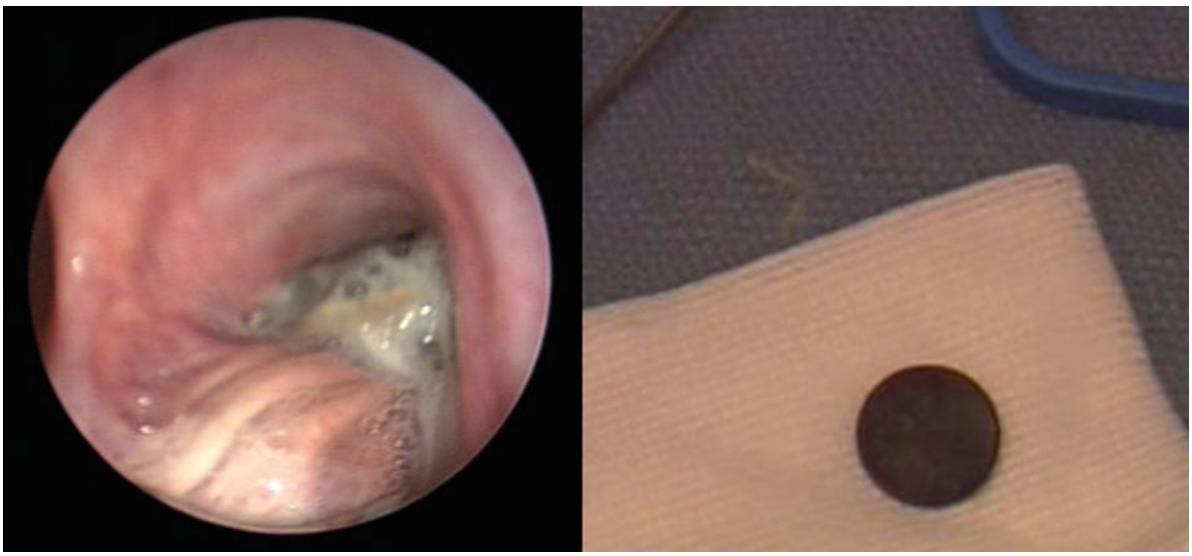


Fig. 46.4 Coin impacted in the airway and post removal. (Courtesy H. Colt and S. Murgu, UC Irvine, www.bronchoscopy.org)

intermittent yet persistent cough, recurrent respiratory tract infections, or an asthmatic syndrome. Importantly, 25% of patients may present with no symptoms. Because an extensive history may reveal the likely diagnosis in only half of all patients, the highest index of suspicion must be maintained in order to pursue a proper diagnostic paradigm.

The examination of the patient may not reveal anything suggestive of a foreign body if the material is lodged distally. Alternatively, auscultation may reveal stridor, wheezing, rales, or simply decreased breath sounds.

Significant delay in presentation occurs for any number of reasons in some cases. Although it is not uncommon for delays in diagnosis to extend for weeks to months, years may even pass, with the longest delay reported by Chevalier Jackson at a staggering 45 years. Furthermore, delays in therapy may also arise. An extreme example was a diver who aspirated foreign body while working at a United Kingdom research base during the Antarctic winter that prohibited early removal or evacuation. Most patients do not encounter such hurdles; however, many rural hospitals and facilities do not have the local expertise, therefore necessitating transfer. Depending upon the type of foreign body, its location, and the inflammatory response, even larger centers may not have the experienced team to remove an impacted object, potentiating the delays before removal.

Complications of Long-Standing Foreign Bodies

As noted previously, a foreign body may incite a local inflammatory response or proliferation of granulation tissue. Secondary infectious complications occur due to impacted objects. Recurrent post-obstructive pneumonias or lung abscess can develop. Unusual infections including endobronchial actinomycosis and botryomycosis have been described. Regions subjected to chronic inflammation or infection may develop bronchiectasis or bronchomalacia. Bronchiectasis develops in 25% of children in whom the diagnosis was delayed greater than a month. The inflorescences of many grasses including “Timothy grass” are a well-known cause of bronchiectasis. Erosion through the bronchial wall may create a fistula. Foreign bodies have been reported to have migrated into the pleural space, the pericardium, and even into the intestine. Aspiration of some medications or chronic inflammatory states may cause stricture rather than bronchiectasis. Iron tablets can cause a severe chemical burn to the bronchial tree with subsequent necrosis and cicatricial scarring.

Migration of long-standing extrapulmonary foreign bodies may also cause chronic infection once in the airway. Such was the case of an infantry soldier who was found with a bullet in his airway after being shot 53 years before during World War II.

Yildizeli and associates evaluated an animal model for radiographic and histological correlation. They found a progressive effect of leukocyte infiltration with edema followed by mononuclear cells and macrophages. This infiltrative process created fibrosis and bronchial cartilage destruction. Tang and colleagues showed that foreign bodies may incite airway remodeling via matrix metalloproteinase's and hydroxyproline.

Radiographic Investigation

While some of the most impressive images of foreign bodies are radiographic, such as knife blade or large screw in the main stem (see Fig. 46.1), most radiographic studies are of limited diagnostic assistance. Radiographic evaluation should never be used to exclude an airway foreign body. Overall, CT scanning is much better for identifying potential airway objects. However, as reported by Zissin, false positives do occur. Routine chest radiography and fluoroscopy may be helpful when looking for indirect evidence of obstruction but must never be used as an independent imaging modality. Most foreign bodies are radiolucent and hence not clearly visible on routine imaging. In the experience reported by Srppnath and later by Mise, only 2–7% of foreign bodies were radio-opaque on routine chest radiography. Indirect evidence to suggest a foreign body includes nonspecific signs such as segmental or lobar atelectasis, air trapping, infiltrates/consolidation, subcutaneous emphysema, or mediastinal shift. Only 4% had normal chest radiographs in Srppnath's retrospective series. These changes are best seen when comparing full inhalation and expiratory imaging. Newer multi-slice CTs and virtual bronchoscopy may provide clearer insight, as demonstrated by Cho and Sodhi, respectively.

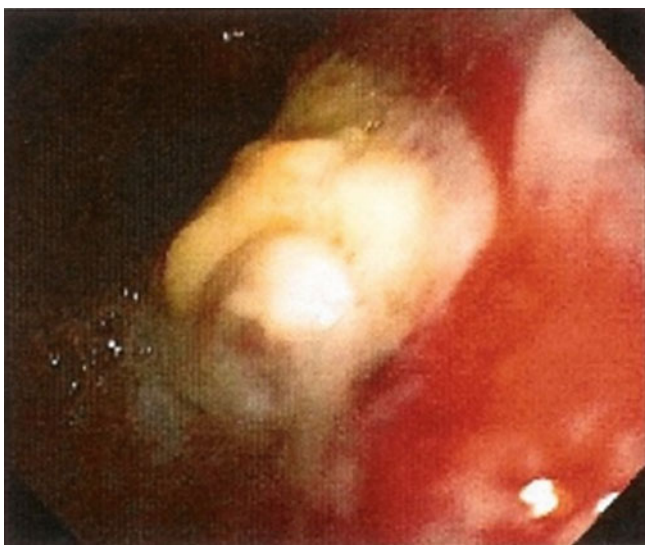


Fig. 46.5 Broncholith eroding into a main stem airway. (Courtesy Daniel Sterman, MD)

Unusual anatomy may suggest a bronchogenic carcinoma. A mass near the trachea has been reported to be a foreign body with inflammatory changes in a tracheal bronchus. While this is a rare case, multiple reports show endoluminal biopsies for endobronchial cancer with foreign material and inflammation. Therefore, while rare in comparison to lung carcinoma, it is possible for an "endobronchial tumor" or "peripheral lung mass" seen on CT imaging to be a complication of an aspirated foreign body.

When presented with a nondiagnostic imaging evaluation, any history remotely suggestive of an aspirated foreign body warrants an airway inspection with flexible bronchoscopy.

Therapeutic Approaches

Bronchial anatomy predisposes the intermediate bronchus and right lower lobe to the majority of aspirations (see Table 46.2). This is due to its larger size and its more vertical orientation when compared to the left main stem. However, anatomy and body position during the aspiration event may alter this predisposition. In fact, any lobe, segment, or subsegment may be the site of impaction. The seven rules of bronchoscopy should always be considered when dealing with bronchoscopic removal of an airway foreign body (see Table 46.3).

In patients who present with stridor or severe dyspnea suggestive of proximal obstruction, heliox should be utilized. The titration of heliox can be based upon the predominant effect on the respiratory system. If the minute volume is most affected, a higher percentage of helium (80:20) may be more useful to reduce the viscosity of the gas. Patients with combined hypoxemia and ventilatory defects benefit from lower percentages of helium and increased oxygen. Use of 30–50% F_IO_2 may maximally balance oxygen needs and improved gas flow.

Preparation

Should all foreign bodies be removed? Chevalier Jackson reported a success rate of 98% and a consequent reduction in mortality from 24% to 2% using rigid bronchoscopy. As a general rule, all foreign bodies should be removed. Clinical expertise and an experienced team will substantially increase the likelihood of success. With the proper team, correct instrumentation, and an experienced bronchoscopist, virtually all foreign bodies are safely and successfully removed. While a multidisciplinary approach is helpful in most circumstances, the requirement for thoracotomy is minimal.

Table 46.2 Location of foreign body

	Trachea (%)	Right (%)	RMS/RBI (%)	RUL	RML (%)	RLL (%)	Left (%)	LMS (%)	LUL (%)	LLL (%)	Carina (%)
Zissin		74	16		11	47	26	11	4	11	
Athanasiadi	4	44	35			9	52	30	13	9	5
Eroglu	10.90	52.70					30				

Table 46.3 Mehta's seven rules of successful bronchoscopy

1	Complications occur when a bronchoscopy is performed for unclear reasons or the wrong indication
2	Preparation ensures 50% success rate
3	Bronchoscopy is a three-handed procedure
4	A good bronchoscopist has excellent skills, but an excellent bronchoscopist is surrounded by excellent support and backup
5	Time and commitment are essential
6	Know your limitations
7	Every case should be viewed as a teaching and training opportunity

In many cases, moderate sedation with opiates and benzodiazepines is insufficient. This is particularly true when there may be a need to change from flexible to rigid bronchoscopy. Monitored anesthesia care (MAC) or general anesthesia is frequently more appropriate. Consulting anesthesia is frequently a value-added use of time. Involving anesthesia allows safe titration of the sedation requirements as the procedure warrants. Furthermore, it allows the endoscopist to focus on the task at hand. When compared to inhaled anesthetics, total intravenous anesthesia (TIVA) is very helpful in maintaining a stable level of anesthesia when alternating between airway interventions and the potential tidal volume loss encountered during rigid bronchoscopy.

It is always best to use the oral approach rather than the trans-nasal approach because the foreign body may not traverse the turbinate's in the nose. Selection of the appropriate airway support is important. The choice of direct bronchoscopy, laryngeal mask airway, or endotracheal intubation should be based upon the medical condition of the patient and the foreign body being removed. In addition, the pre-sedation evaluation of the airway is critical even if intubation is not planned. What difficulties may be encountered if the patient requires urgent intubation or rigid bronchoscopic intubation? Pre-procedural assessment of the Mallampati score, thyromental distance, mandibular opening, and cervical range of motion are all important to the pre-procedural planning. Evaluation for loose teeth is also critical. Notwithstanding the medical-legal need to document their presence, it is important to understand the potential to leave a new foreign body in the airway.

Flexible Versus Rigid Bronchoscopy

Much has been written regarding the proper choice of bronchoscope. The standard of care had been rigid bronchoscopy for all foreign bodies. With the advent of large working channel bronchoscopes and a wider array of instruments, retrieval of impacted objects has become routine with the flexible bronchoscope. A success rate of 86% has been reported with the use of flexible bronchoscopy. There are institutional and practice preferences that drive the approach. For most patients, the decision must be made, taking into consideration both operator comfort and the circumstances presented in each unique situation. In patients with stridor and partially obstructing tracheal foreign bodies, a rigid bronchoscope is often the better instrument. In some cases, pushing the object distally to initially improve airflow is required. This may be difficult with a flexible bronchoscope. Any patient presenting with respiratory failure is best managed with a rigid bronchoscope. Operator inexperience or lack of training must never be the reason for failing to use a rigid bronchoscope when one is required. The patient should be transferred to a center with an experienced team before complications ensue, impairing removal or patient safety.

Removal Procedure

Regardless of which endoscopic approach is taken, an initial surveillance of the entire visible tracheobronchial is required. The exception to this rule is when tracheal foreign bodies are found or the patient is in extremis. If able, the bronchoscopist should understand what other anatomical variations or potential secondary foreign bodies are present that may complicate the primary procedural goal.

Proper preparation is a significant indicator of success, and this includes the airway itself. As noted previously, granulation tissue may initially suggest a tumor or may limit the approach to an impacted foreign body. When presented with exuberant granulation tissue, several potential approaches may be helpful. Preparing the airway is critical in some circumstances. Granulation may be reduced by use of argon plasma coagulation or low wattage use of the Nd:YAG laser. Caution must be observed when using thermal techniques if one is unsure of the foreign body and its inflammability.

When available, cryotherapy may also be utilized to reduce the granulation tissue and limit the risk of fire with unknown materials. Endobronchial injections may be beneficial. Use of a 23–25 gauge sclerotherapy needle with 1:10,000 epinephrine can be helpful in preemptively controlling bleeding from these vascular tissues. Intralesional and submucosal injection of triamcinolone acetonide can help reduce the inflammatory response if waiting for a second procedure is a viable option.

When preparing to remove an object, consideration of its substance must be undertaken. Different instrumentation will be required for soft material in comparison to metallic or calcified objects. Similarly, if an object is easily fractured, the operator must limit the possibility of pieces breaking off and moving distally, preventing complete removal.

Grasping Forceps and Graspers

There are a number of different forceps on the market that can be useful in retrieving airway objects. Biopsy forceps are almost universally of limited value. Whether using a flexible or rigid bronchoscope, the design of the forceps is very similar. The variation is the size and the grasping force. The degrees of freedom for operating in the airway are limited. Forceps are generally dividable into two categories based upon jaw movement. Single action forceps have one movable jaw and a stationary jaw. The dual action forceps have two mobile jaws that open at roughly 40° from the original plane. There are benefits to both depending upon the material and the airway location. In addition, there are several varieties of grasping surface. There are coarse serrations, finer serrations, typically with a broader surface area (peanut forceps), and toothed forceps. Most forceps are straight; however, there are curved, serrated grasping forceps available for use with a rigid bronchoscope. Rotatable instrument designs are available for both flexible and rigid bronchoscopy. However, most rotatable forceps require rigid bronchoscopy (see Fig. 46.10). It should be noted that use of various instruments is limited or expanded by the diameter of the working channel. Using a therapeutic bronchoscope with a 2.8–3.2-mm working channel opens the utilization of almost all current gastrointestinal endoscopic forceps, graspers, and baskets.

The rigid bronchoscope also permits optical forceps to be utilized. This increases the visualization of the object when maneuvering and grasping by placing the telescope at the distal end and having the forceps angled to bring the grasping action into direct visualization.

There are several graspers on the market, utilizing from two to five grasping fingers. These can be useful in grasping objects too large for the standard jaws of flexible instruments. Forceps are also available with soft latex-free rubber-coated jaw to assist in removing fine objects such as needles.

The selection for any procedure is dictated by institutional availability, location of the object, and the material to be removed. Individual experience will determine the most appropriate instrument.

Snares

Snares are loops of wire deployed through a flexible tube via the working channel. The snares vary by deployed diameter, wire stiffness, wire design (twisted and smooth), and the availability of electrocautery. A snare may be used to encircle many objects of varying shape and using the operating handle to grasp it tightly. Electrocautery would rarely be used in foreign body retrieval; however, cautery snares may be safely utilized when not attached to an electrosurgical generator. Electrocautery may be useful in reducing the volume of granulation tissue.

Baskets

Baskets are essentially more complex snares, without electrocautery potential. There are an increasing number and variety of baskets available for foreign body retrieval. Many of these have been designed for removal of resected colonic polyps but are very adept at grasping many foreign materials (Fig. 46.6). The difficulty with many of these is their size, with some so large as to preclude effective use in the airway. Almost universally, these baskets are small, deployable, and retractable cages created with three or more wires. They vary in structure by their overall shape, wire stiffness, and tip structure, as well as wire count. Some are spiraled and others more half clam shelled (see Fig. 46.7). All designs offer good ability to capture and secure an object. Utility is based upon the size and location of the foreign body and the operators' experience. The lack of a "tip" on one currently available device makes it useful in more distal airways or at airway trifurcations (see Fig. 46.8).

When using these baskets, care must be taken with softer or macerated materials. The wires have the ability to cut through some objects, simply creating three, four, or more foreign bodies to retrieve. One potential solution to these softer materials is the use of retrieval nets. These are essentially snares that have fine netting secured to the snare wire (see Fig. 46.7). This allows a very flexible netting to encompass the object providing a secure hold. Care must still be exercised, as some very gelatinous materials may still be forced through the netting.

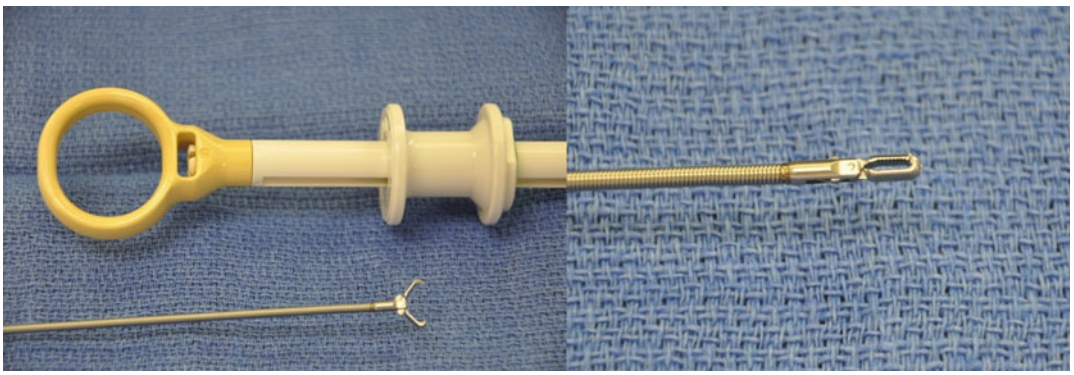


Fig. 46.6 Flexible grasping forceps open and closed

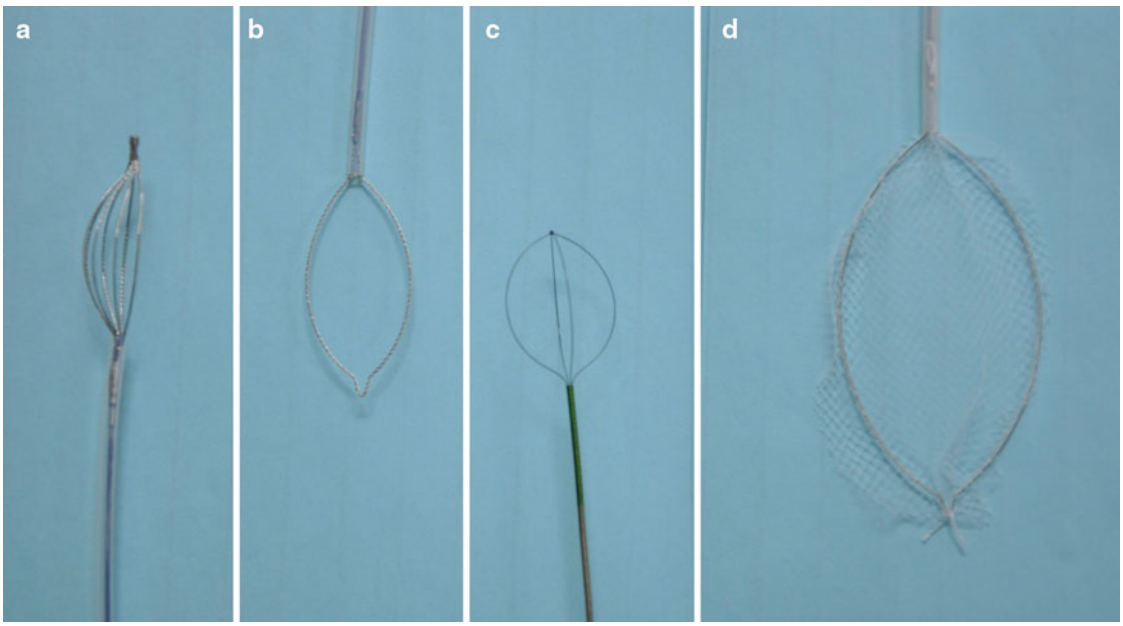


Fig. 46.7 Flexible bronchoscopic snares and baskets. (**a**) Twister™ rotatable polyp retrieval (Boston Scientific, Natick, MA). (**b**) Rotatable snare 13 mm (Boston Scientific, Natick, MA). (**c**) ZeroTip™ airway basket (Boston Scientific, Natick, MA). (**d**) Roth Net™ (US endoscopy, Mentor, OH)

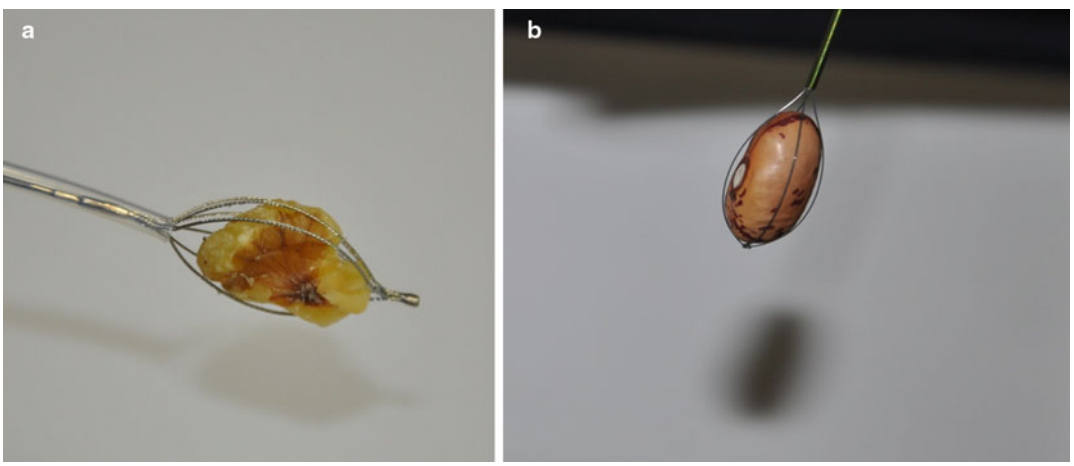


Fig. 46.8 (**a**) Twister™ rotatable polyp retrieval (Boston Scientific, Natick, MA.) basket with a walnut. (**b**) Zero Tip™ (Boston Scientific, Natick, MA.) basket with a bean

Cryotherapy

Cryotherapy probes may be of great assistance in management of certain foreign bodies. Not only can they help with granulation tissue but those objects with high water content can be frozen to the therapeutic probe and removed, frequently intact. These foreign bodies typically include fruits, vegetables, and insects (see Fig. 46.9). Occasionally, a material has been saturated with airway secretions or can be saturated with sterile water and frozen to the cryoprobe. Nuts, metallic, or ceramic objects commonly are resistant to this technique. However, there are some anecdotal reports of using sterile water to freeze an "ice block" around the object, hence allowing removal with the probe. The cryoprobe can be very helpful in removal of these obstructive mucoid plugs. Further case reports have shown the potential to remove broncholiths with a cryoprobe.

Embolectomy Balloons

Vascular embolectomy balloons are used to move distal to an impacted object and upon inflation enable it to be pulled into a more proximal airway or dislodged. The importance of maneuvering a distal foreign body into more proximal airways cannot be underestimated. Sizes 4–7 are most frequently helpful. These balloons are commonly inflated with saline or contrast media rather than air to create a more rigid platform. When the bronchoscopist is unable to get a solid grasp on an object, using the balloon may be helpful to position it into a more favorable location. When used through a rigid bronchoscope, the balloon may be positioned distally to prevent further migration while using other instrumentation to grasp the object. Balloons are subject to rupture, particularly when used with sharp objects such as teeth or crowns. Caution should be exercised to prevent rupture or loss of fragments after rupture of a balloon, creating a secondary foreign body. In very unusual circumstances, the controlled radial expansion balloons may be helpful; however, the balloon length almost always precludes their safe deployment and utility.

In cases where the operator wants to maneuver an object into better position but is concerned about balloon integrity, an articulated endobronchial curette can be used. These curettes allow passage via the working channel of a thin, metallic probe. This probe is articulated at one or two locations, allowing a fingerlike motion once past the object. The sharper edge of the curette helps with manipulating the object. These instruments are also rotatable, allowing finer manipulation.

Nd: YAG Laser

The medical use of lasers is covered in detail in other chapters. The use of a laser in the management of foreign bodies is somewhat limited. As described previously, a lower wattage of 10–20 W may be used to judiciously reduce granulation tissue. Care must be undertaken to avoid airway fire, by not only reducing the F_IO_2 to less than 40% but also understanding the potential for the foreign body to ignite.

Another potential use of the laser is to help with manipulation and removal of the object. The Nd:YAG laser is able to cut many metals. Cutting a pin or needle that is imbedded may make it more easily removable and induce less tissue trauma. This use of the laser requires higher wattage; however, there are no defined wattage settings for this purpose. Many Nd:YAG lasers have maximal wattage settings up to 100 W. Use of wattages from 40 to 60 W or greater may be required. In addition, closer approximation of the laser fiber to the material, decreasing the circumscribed area of the beam, hence increasing the power density, should be considered. Changing the pulse duration may also be needed. Cautious titration up, by effect, is advisable. Understanding the tissue effects of the laser, the concept of power density, and careful aiming are all critical to safe utilization of the laser in this manner. Initial unseen injury from deeper more absorbent tissues or from reflected laser light must be considered.

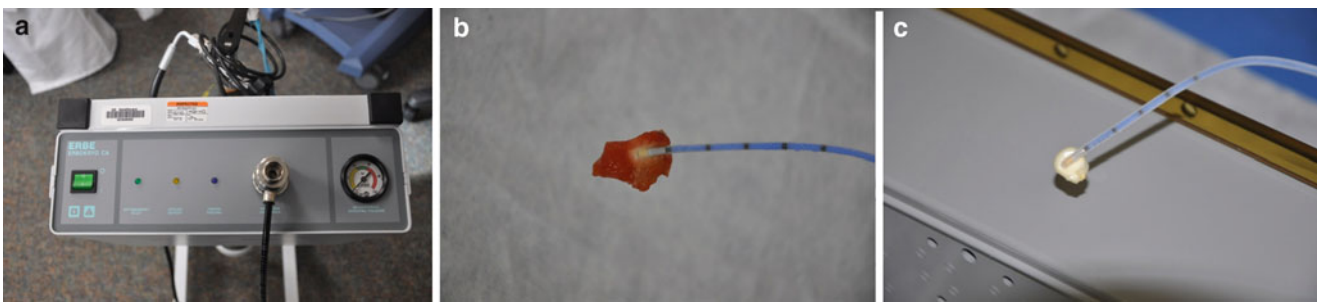


Fig. 46.9 Cryotherapy. (**a**) ERBE cryotherapy unit. (ERBE-USA Marietta, GA). (**b**) Tomato frozen to tip of Cryoprobe. (**c**) Corn frozen to the cryoprobe

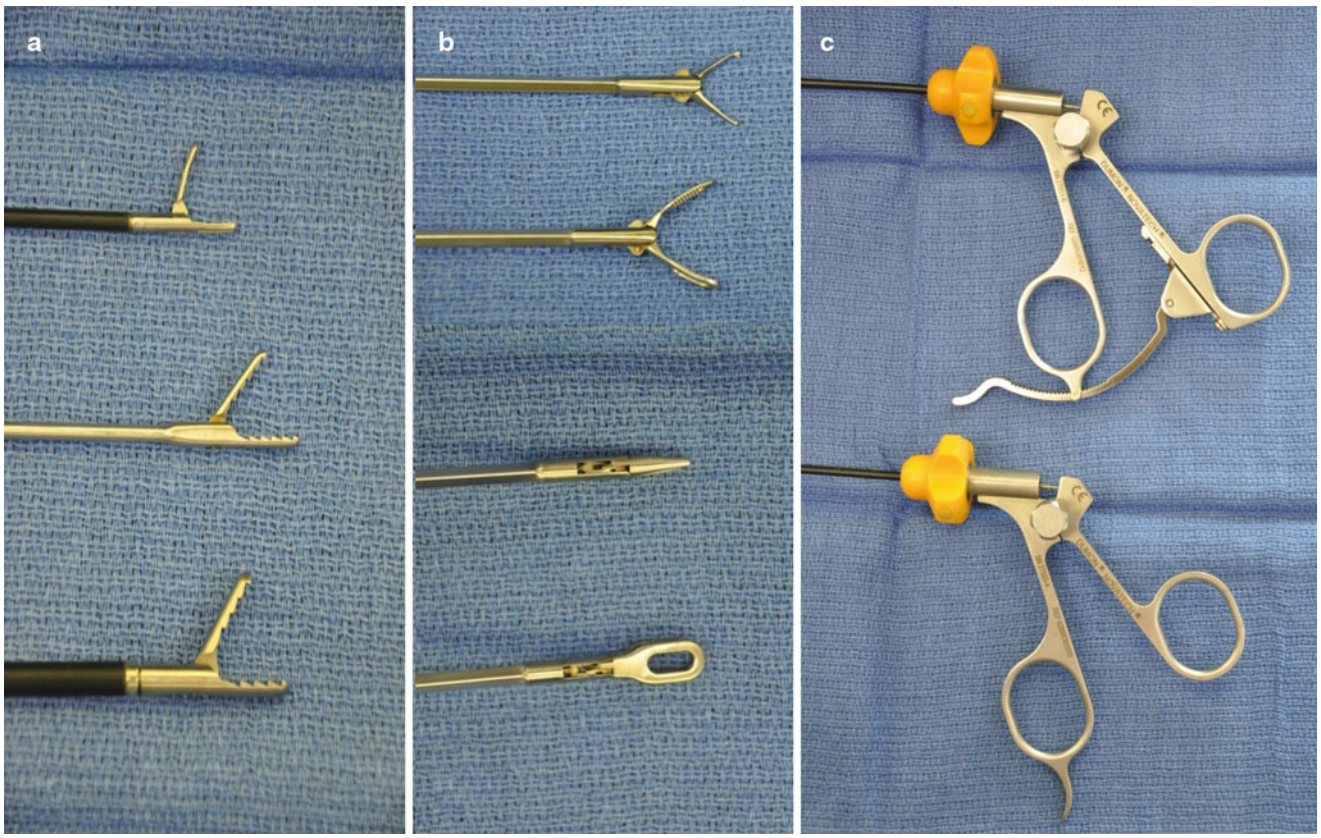


Fig. 46.10 Rigid bronchoscopic instruments. (**a**) *Top–Bottom*: fine serrated forceps, coarse serrated forceps, heavy coarse serrated forceps. (**b**) *Top–Bottom*: toothed grasper (*side view*), peanut grasper (*side view*), toothed grasper (*top view*), peanut grasper (*top view*). (**c**) *Top–Bottom*: ratcheting and non-ratcheting handles. The *yellow* knob allows rotation of the forceps without rotating the operator's hand

Management of large broncholiths may be difficult but can be safely removed. There are several reports in the literature that suggest the utility of laser therapy. Broncholiths have been fractured into smaller, more easily extracted objects with the Nd:YAG and the holmium laser. It may be that the holmium laser is the better approach based upon its history in urologic calculi; however, data is very limited.

Distal Impaction

When foreign bodies are distal, the challenge is greater. Small radiolucent objects may not be removable endoscopically. As previously noted, an object that is being pushed distally in removal attempts may be pulled proximally by use of a vascular embolectomy catheter. When radiopaque objects are not visible, use of interventional radiologic instruments may be helpful. As an example, the localization by guidewire and snare with an Amplatz GooseNeck® snare (ev3 Endovascular, Inc., Plymouth, MN) has been reported by Nalaboff and colleagues. The use of navigation bronchoscopy to these distally lodged foreign bodies has yet to be evaluated.

Surgery

Surgery is the avenue of last resort for virtually all foreign bodies. Thoracotomy with bronchotomy or lobectomy is rarely required. The indication for surgery would include those objects that have induced serious airway injury that must be repaired or will probably do so in an attempted removal. Rare objects that cannot be removed by bronchoscopy will require surgical intervention. Patients with long-standing foreign bodies that have destroyed significant parenchyma or those causing unremitting infection after removal may require surgical resection. Mediastinoscopy has been used in case reports to assist in removal of sharp foreign bodies that have penetrated the anterior mediastinum. This approach may avoid a full thoracotomy.

Complications of Therapy

Intraoperative complications are very unusual but can occur even with a highly trained proceduralist. Being aware of the potential occurrence and rapid determination of its presence

is critical to mitigating the complication. Care must always be exercised not to push a foreign body too distal in the attempt to remove it. In addition, it is possible to lose control of an object more proximally after it is retrieved. This creates a potential for rapid decompensation of the patients' respiratory status. If a foreign body becomes stuck while removing, it must be pushed distally immediately if causing central airway obstruction. These objects may then migrate into other locations.

Although rare, disruption of the airway may occur either because of a rigid bronchoscopy or because of removal attempts. Airway perforations are best evaluated with an experienced thoracic surgeon. Sharp or rigid objects such as needles, pins, and metallic objects increase the risk of airway penetration. Much more prevalent than airway perforation is the risk of bleeding with eroding broncholiths, ingrown objects, or granulation tissue.

While uncommon, the ability to control significant bleeding and protect ventilatory function is required. Management of life-threatening intraoperative hemorrhage may require endobronchial blocker placement. This can be complicated by the location of the foreign body. Rigid bronchoscopy is frequently required to control massive airway bleeding. The bronchoscopist should have contemplated an action plan at the start of the therapeutic attempts based upon the airway anatomy and location of the object.

Flooding of the airway with purulent material after decompressing a post-obstructive pneumonia is also a possibility. Decanting of this fluid into the contra-lateral lung can be catastrophic. If there is preoperative concern regarding the potential for post-obstructive pus, the bronchoscopy should be performed with an attempt to reduce the potential of decanting the drainage. This can be accomplished with use of the safety position or with rotation of the OR bed into an oblique angle with the involved lung down.

Laser use can cause significant damage if higher wattage is utilized. This deeper damage may not be initially visible, and postoperative reevaluation may be warranted.

One potential complication of therapy is the potential for retained foreign bodies. This may develop because of loss of some primary material, iatrogenic loss of instruments (balloon pieces), or failure to diagnose a second foreign body. This may be the most troublesome because the initial high index of suspicion is now significantly reduced. Ensuring a clear airway by methodical evaluation of all visualizable airways is crucial.

Conclusion

While the majority of aspirated foreign bodies involve children, a significant number of adults experience inhalation of foreign material. A high index of suspicion must be maintained. When clinical suspicion suggests a potential foreign body in the tracheal bronchial tree, negative imaging must never exclude the diagnosis. Chevalier Jackson stated "Do not fail to search endoscopically for a foreign body in all cases of doubt." Furthermore, once airway foreign bodies are diagnosed, exhaustive efforts should be undertaken to remove the object to mitigate long-term complications.

Flexible bronchoscopy can be safely and successfully utilized in the majority of cases. However, if there is any doubt as to the ability to remove the foreign body with a flexible scope or the risk of intraoperative complications, the bronchoscopist must be prepared and facile with a rigid bronchoscope. Rigid bronchoscopy is the fail safe backup for the vast majority of difficult extractions. Surgery, including bronchotomy and lobectomy, should be rarely required.

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Resection and Reconstruction of Central Airways

47

Hendrik C. Dienemann

Trachea

Stenosis after intubation or a tracheotomy is the most frequent indication for resection and reconstruction of the central airways. A pressure necrosis at different points of the trachea as a result of contact with the endotracheal tube, the tracheotomy tube, or with the inflated cuff is a common cause for the occurrence of these lesions. Even the existence of mucosal ischemia for just a few hours can initiate a repair process, the course of which is determined by the type and severity of the affected section. On the level of the tracheostoma, obstructive granulations might develop, from which typically ventral scar strictures emerge. On the level of the inflatable cuff, there are circular mucosal erosions with consecutive, circumferential scars and differing degrees of development. According to the extent and/or depth of the pressure injury, weblike, short stenoses with preserved cartilage develop, or hourglass-shaped, long stenoses with the entire wall destroyed (refer to Figs. 47.1 and 47.2). More seldom does malacia occur resulting from cartilage atrophy; a combination of fixed stenosis and malacia has also been observed.

Clinic/Symptoms

As stenoses, apart from granulations, generally develop slowly, they are often not diagnosed until at an advanced stage. Therefore, many patients have adapted to high-degree obstruction. Only when the diameter is reduced to 5–6 mm does a significant drop in the peak flow appear.

Patients with pertinent postintubation stenoses have dyspnea on exertion or dyspnea at rest with noticeable stridor. These patients are often mistaken for asthma sufferers, particularly when the X-ray image does not indicate any abnormalities. Inspiratory stridor usually indicates a fixed stenosis or malacia of the cervical trachea, whereas intrathoracic lesions are accompanied by expiratory stridor.

Diagnosis

It should be clarified with every patient exhibiting stridor after recent intubation whether a scar stenosis can be excluded. A thoracic CT scan with 3-D reconstruction provides an overview of the degree and extension of the stenosis, permitting an evaluation of operability and reconstruction planning with the exposition of an intact trachea. A flexible tracheoscopy should confirm the findings; however, it can be postponed until the time of operation if there is a clear indication to operate and convincing images are available. High-degree scar stenoses that require emergency intervention may be removed with a rigid bronchoscopy, or a tracheostomy with possible subsequent resection may be necessary to safeguard the airways. Should a malacic lesion – which may also result from cuff damage – be suspected primarily, then an endoscopy ought to be done with spontaneous respiration. Systemic lesions like Wegener's granulomatosis, relapsing polychondritis, tuberculosis, or amyloidosis may involve the trachea and induce diffuse narrowing. These patients should undergo systemic treatment. Only rarely a segmental resection may become necessary.

Acute Obstruction

An endoscopy should be performed in case of acute obstruction by a postintubation stenosis, ideally using a jet ventilation catheter. The introduction of a rigid endoscope to the point of the stenosis is followed by suctioning secretions and subsequent cautious dilatation of the constriction by sliding forward the dilatator with increasing diameter or the rigid bronchoscope itself. The dilatation is to be effected with

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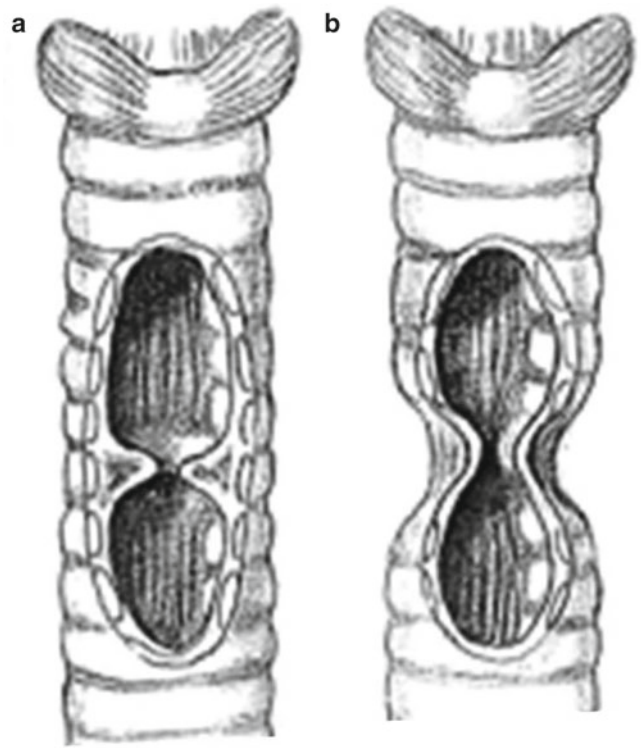

Fig. 47.1 (**a**) Weblike postintubation stenosis with preserved cartilage. Laser resection may be successful; however, recurrence is likely to occur; (**b**) hourglass-like postintubation stenosis with destruction of all layers. Segmental resection indicated (Reprinted with permission from Heberer et al. editors. Lunge und mediastinum, Springer; 1991, Fig. 18.58)

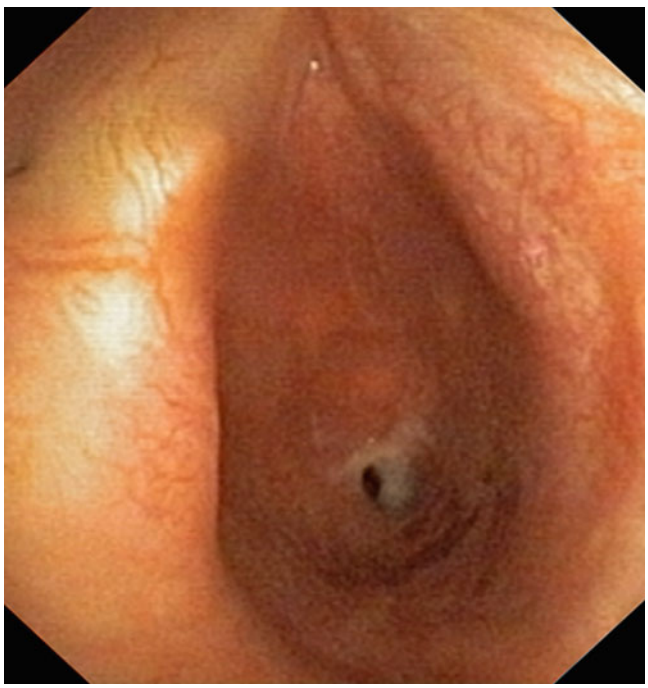

Fig. 47.2 Weblike postintubation stenosis 2.5 cm below the vocal cords, endoscopic aspect

rotating movements to avoid a rupture of the usually less rigid posterior wall. If an instrument the size of at least 3 mm can be introduced, then sufficient lumen width has been achieved for the moment to be able to plan an elective operation. Should this not be feasible, then a tracheotomy must be performed in the case of a cervical lesion, ideally on the level of the stenosis. Airway stenting may be a preliminary option if the patient's condition does not allow for a subsequent surgical procedure. In our opinion, the use of laser is contraindicated as it causes even more scars and strictures. Solely in case of very short, weblike strictures or when predominantly granulation tissue constricts the lumen, can a bougienage or removal by laser provide permanent success. All in all, the less time that passes after the triggering trauma, the greater the chances are of a permanent correction.

Surgical Principles

The definitive therapy of a fixed or postintubation stenosis, which has been repeatedly dilatated without success, is surgical resection and end-to-end reconstruction, the same being valid for stenoses in connection with a tracheostoma. Reconstruction can be performed in an emergency if circumstances require this. A delay of the operation is advisable if there are significant inflammatory changes, if the patient cannot be withdrawn from the respirator, or if the necessary cooperation on the part of the patient cannot be anticipated for other reasons.

Practically all postintubation stenoses can be treated surgically with success if they are operated on in the primary instance and do not initially undergo repeated conservative measures. If short, softened sections in combination with a stenosis occur, these will be integrated into the resection. Longer, softened segments have to be treated with a stent, T-tube, or external stabilization, depending on the functional significance.

Access to the upper two-thirds of the trachea is achieved through a collar incision which is extended caudally by a median incision to the upper border of the manubrium.

If a tracheostoma is to be removed at the same time, the incision takes place at the level of the stoma. A partial sternotomy can follow if needed. The lower third of the trachea may be reached equally well through a complete sternotomy or a right-sided thoracotomy in the third or fourth intercostal space. The preparation of the trachea must be effected along the immediate wall contours so as not to endanger the Nn. recurrentes. An exposition of the nerves should be refrained from any case in view of the benign processes. With transsternal access, the supra-aortic branches may not be exposed out of their connective tissue, as this might otherwise promote arrosion bleeding.

The size and extent of the constriction must be determined exactly with the endoscope because the extension of the

lesion cannot always be reliably determined intraoperatively. In this case, the upper and lower end of the lesion must be marked under endoscopic control with an aspiration needle. After installing the jet ventilation catheter, a transection is performed, at the lower end in the case of cranial stenoses and at the upper end in the case of caudal stenoses, and mobilization out of the environment is carried out with visual control to the other end of the stenosis. The circumferential dissection of the trachea at the proximal and distal border of the defect should not exceed 1 cm in order not to endanger the blood circulation of the anastomosis. After affixing a stay suture on the distal stump, mobilization with a cranial pull is performed and the loose connective tissue ventral to the trachea down to the bifurcation is severed or pushed aside. Now the patient's head is ventrally flexed by the anesthetist and fixed in this position with pillows. In this way, defects of up to 5 cm can be bridged without danger. Running sutures are placed along the posterior wall with PDS 4/0 (Ethicon, USA); however, the adaptation is not yet fully completed to avoid ripping of the sutures. Only when the corner sutures have been inserted and with a pull on the stay sutures will the edges of the posterior wall be adapted and the running sutures of the posterior wall connected to the corner sutures. All interrupted sutures for the anterior wall are placed and tied one after another. Before this, blood coagulation and secretions should be removed once again from the bronchial system and the transition from jet ventilation to ventilation with the tracheal tube prepared. In no case may the tube cuff be placed at the level of the anastomosis. A leakage test is obligatory. For this purpose, ventilation pressure of 30 cm H_2O is built up while the operational field undergoes rinsing with a saline solution. Early extubation of the patient is desired. Tracheal release maneuvers are special techniques that permit a reduction of anastomotic tension. The aforementioned dissection of the pretracheal compartment down to the bifurcation and ventral head flexion is obligatory. Only in very rare cases is a hilar or laryngeal release maneuver applied.

Results

In the greatest published series of postintubation stenoses and resection including reconstruction (Grillo, Pearson), good or very good results for over 90% of the patients were achieved. Mortality ranged from approximately 2% to 4%; morbidity (anastomosis insufficiency, infection, restenosis) is estimated at 4–10%. In addition to the surgeon's expertise, several different factors influencing complication rates have been determined:

(a) Every surgical pretreatment significantly aggravates the operation and results in twice the number of cases of mortality. This substantiates the requirement that a competent surgeon should perform the initial operation.
(b) The safest anastomoses are those with an end-to-end connection in the tracheal section. Anastomosis with the cricoid cartilage is riskier with respect to healing, whereby connections between the trachea and thyroid bear even greater risks.
(c) A contraindication for resection is present with patients under ventilation for a long period of time.

Postoperative problems such as vocal ligament palsy, intralaryngeal swelling, or an edema of the anastomosis may require an immediate or delayed tracheotomy. This is preferably performed below the anastomosis but must be securely covered by a muscle flap with respect to the truncus brachiocephalicus to avoid vascular arrosion.

Restenoses at the level of the anastomosis are rare when expert techniques are employed, absorbable stitching material is used, and the complete resection of the diseased segment is performed. The prophylaxis for stenoses caused by intubation is the correct use of large-volume cuffs. Pertinent complications after a tracheotomy can be avoided if mechanical irritations between the tube and trachea entrance are reduced to a minimum.

Tumors of the Trachea

Adenoid cystic carcinoma and squamous cell carcinoma are the most frequent primary malignant tumors of the trachea, the former often including the main carina. Carcinoids, mucoepidermoid tumors, small cell carcinomas, lymphomas, or benign chondromas are rare. Leading among secondary tumors are carcinomas of the thyroid gland, which often include the subglottic area and the cricoid (refer to Chap. 51). Allowing for the size of the tumor, the best choice of therapy is a tracheal segmental resection (exception: small cell carcinomas, lymphomas) with end-to-end reconstruction (refer to Fig. 47.3a–c). The adenoid cystic carcinoma typically progresses beyond visible limits by spreading submucosally or paratracheally within the perineural lymphatics. In this case, intraoperative specimen examinations are indispensable. The security of the anastomosis, i.e., a tension-free reconstruction, always has priority over microscopically free resection borders, as the tumor occasionally grows very slowly. For this reason, excessive resection focussing solely on radicality is to be avoided.

As far as the radicality aspect goes, an endoscopic-interventional procedure alone is by no means sufficient. Utilizing endoscopy and ultrasound, an exact description of the size of the tumor must be given. The upper two-thirds of the trachea are reached via a cervical incision, the lower third by means of a sternotomy or lateral thoracotomy. The length of the operative specimen may not measure more than half the length of the trachea, and preparation for hilar and laryngeal release maneuvers must be made in case of necessity.

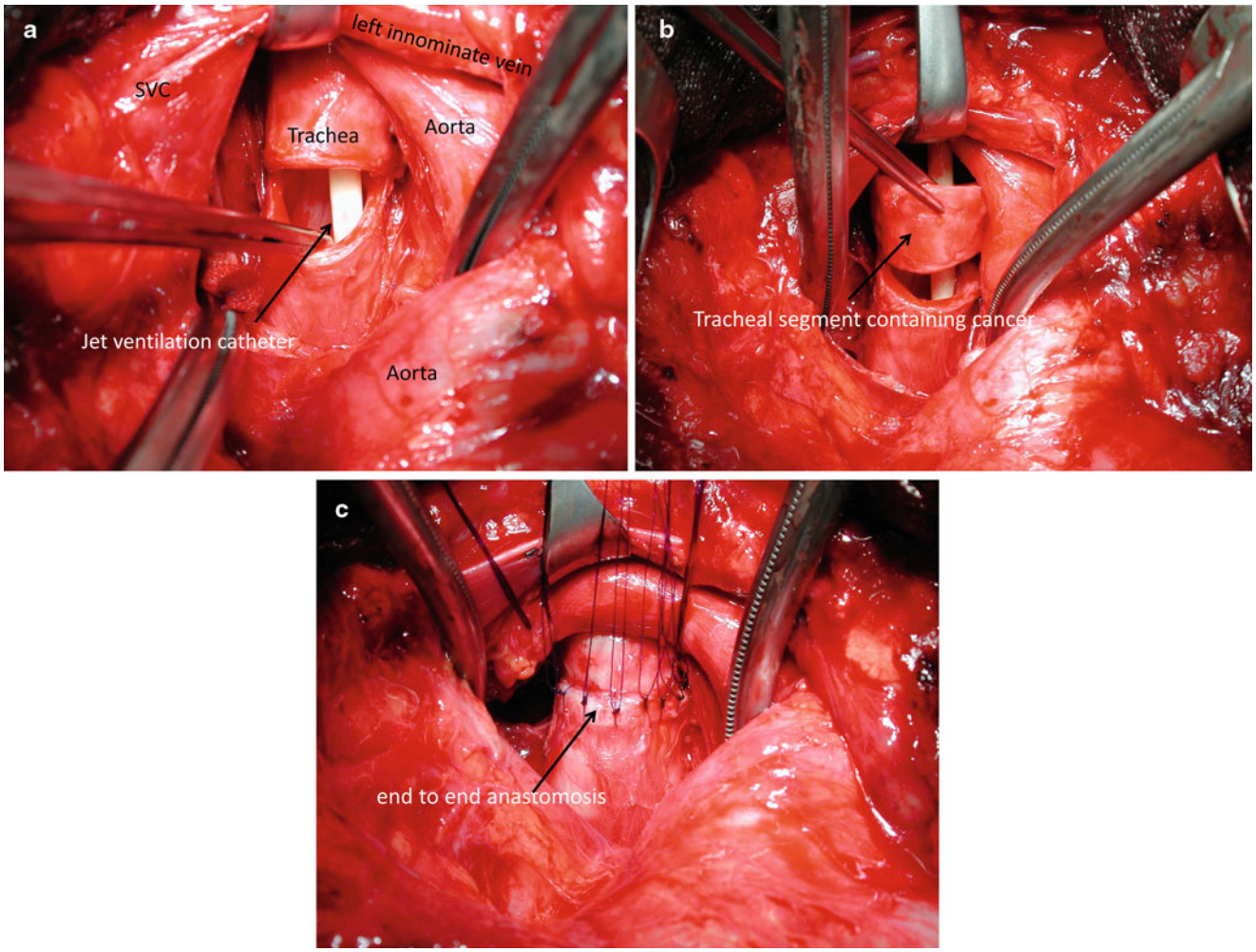

Fig. 47.3 Tracheal tumor (mucoepidermoid tumor) (**a**) Transsternal approach to the distal trachea. Incision below the tumor, jet ventilation catheter visible. (**b**) Tracheal segment with tumor mobilized. (**c**) Tension-free end-to-end anastomosis

Contrary to resection techniques employed with benign stenoses, infiltrated structures in the vicinity of the trachea are also resected en bloc. This can affect mediastinal lymph tissue, segments of the esophagus wall and, upon proven infiltration, the N. laryngeus rec. Otherwise, the surgical principles do not differ from those which are applied in the case of scar stenosis. Operative mortality is 1–2% after a trachea segment resection; however, it is up to 10% when the main carina is included (refer to below). The long-term prognosis is determined by the radicality of the operation and the status of the lymph node involvement. Squamous cell carcinomas have a tendency to relapse after approximately 3 years; adenoid cystic carcinomas are characterized by a much longer tumor-free interval. Tumors with low malignancy such as carcinoids and mucoepidermoid tumors have a very good prognosis as long as the lymph nodes have not been infiltrated.

Carina

Tumors with involvement of the main carina pose a considerable challenge to thoracic surgeons. On the one hand, radical resection needs to be pursued; simultaneously, tension-free anastomoses are of great importance in order to ensure primary healing. A compromised healing of anastomoses is the predominant cause of morbidity and mortality.

Due to the complexity and risks of this procedure, a thorough patient evaluation is mandatory in order to verify technical, functional, and oncological operability. By means of a thoracic CT scan and an autofluorescence bronchoscopy, the local tumor extension needs to be identified. In addition, an endobronchial ultrasound is able to provide information concerning the integrity of the tracheobronchial wall and intramural tumor extension helping with the decision of the length of resection.

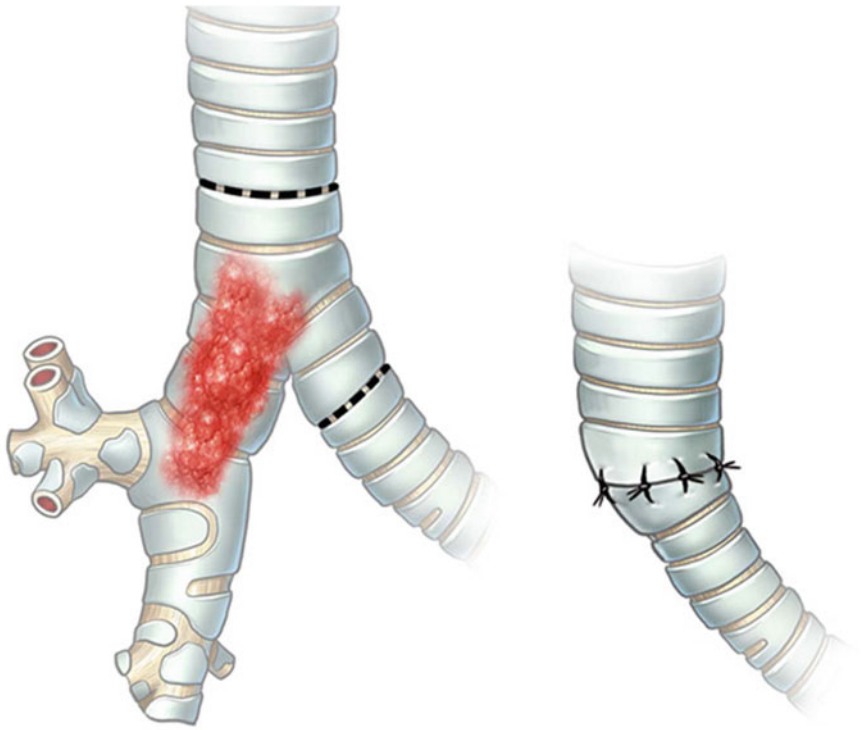

Fig. 47.4 Tumor involving the carina and right main stem bronchus. Principle of reconstruction (Reprinted with permission from Dienemann H et al. editors. Chest surgery Atlas. Springer; 2013.)

Cancer involving the main carina represents a T3 or T4 tumor. For this reason, lymph node metastases and distant metastases have to be excluded by mediastinoscopy and PET scan as well as biopsies if necessary. Regional lymph node infiltration can be missed in a PET scan due to hypermetabolic activity of the primary tumor. An isolated infiltration of a lymph node next to the primary tumor – by definition N2 – should not, however, exclude the patient from the surgical resection especially when detected intraoperatively.

Relative contraindications to surgery are chronic steroid use, resection specimen length of more than 4 cm, or the increased probability of prolonged postoperative mechanical ventilation. If the tumor is narrowing or occluding the central airways, preoperative endoscopic removal is indicated, thus improving ventilation and if necessary facilitating the treatment of postobstructive infection. Use of a long single-lumen endotracheal tube has shown its usefulness. If necessary, it can selectively be introduced into one of the main bronchi. At the same time, one or two jet ventilation catheters can be introduced via this catheter. Double-lumen tubes are generally not useful in this setting. In order to provide sufficient postoperative comfort in terms of pain control, preoperative placement of a peridural catheter is highly recommended.

Most tumorous processes requiring carinal resection include the right-sided bronchial system and are best performed through a thoracotomy in the fourth intercostal space. The transsternal approach provides an excellent overview of the distal trachea and the bifurcational area, yet it requires additional assistance for retraction of the SVC, ascending aorta, and right pulmonary artery. This approach offers the opportunity to perform the bilateral release maneuver as well as the release of the larynx, which is, however, seldomly used. Thoracosternotomy (clamshell approach) offers the optimal access to the bifurcation and both pleural cavities. Nevertheless, this approach is highly invasive and should only be used in patients with excellent general condition when exposure and mobilization via lateral thoracotomy is insufficient. Left-sided thoracotomy in the third or fourth intercostal space is exclusively chosen for left-sided pneumonectomy when no extended mobilization and resection of trachea or right main bronchus are expected.

Techniques of Resection and Reconstruction

(a) *Carina and Right Main Stem Bronchus* (Fig. 47.4)

The most common type of resection involves the carina and right lung; the reconstruction is performed by end-to-end anastomoses between distal trachea and left main bronchus.

Following right lateral thoracotomy in the fourth intercostal space with optional posterolateral extension and opening of the mediastinal pleura, the dissection of mediastinal structures allows assessment of the local tumor extension. Blunt dissection mobilizes trachea and left main bronchus. Close attention has to be paid to the nutritive vessels reaching the trachea laterally. Ipsilateral mediastinal lymph node resection

has to be performed with great care avoiding devascularization of trachea and esophagus. After dividing of the pulmonary artery and the veins, the extent of resection has to be defined. The safety margin should not be less than 0.5–1 cm. After transection of the trachea and left main bronchus, the specimen is removed and sent for frozen section.

A difference in lumen diameter is almost always observed, thus resulting in partially telescoping end-to-end anastomoses. Telescoping should not exceed the breadth of one cartilage ring, and traumatizing the mucosa must be avoided. Once the anastomosis is finished, air leaks can be excluded by underwater testing. Additional coverage of the suture is advised in order to support the healing process. Intercostal muscle, diaphragm, mediastinal fat including thymic tissue, anterior serrated muscle, pericardium, or pleura can be used.

If leakage occurs, it may be explained by telescoping exceeding more than one cartilage.

In this case, removal of suture material followed by a complete new construction of the anastomoses is needed. If incomplete adaptation due to inadequate traction is causing leakage, blunt mobilization of the trachea has to be extended cranially and at the same time a flexion of the head is helpful. Pledgets may be used as a reinforcement to prevent sutures from cutting through the tracheal wall. If the middle and lower lobe can be preserved, an end-to-side anastomosis of the bronchus intermedius into the left main stem bronchus or into the trachea is an easy and safe alternative in comparison to a side-to-side anastomosis of the bronchus intermedius and the left main stem bronchus and consecutive end-to-end anastomosis with the trachea. The implantation has to be performed in the cartilaginous part of the circumference due to lack of stability of the posterior portion. The distance of this anastomosis should be at least 1 cm away from the end-to-end anastomosis in order to avoid interference.

(b) *Carina* (Figs. 47.5 and 47.6a, b)

In case of limited involvement of the carina, the lung parenchyma may be completely preserved. The best overview of the tracheal bifurcation is obtained through the transsternal, transmediastinal approach. Following approximation of the main stem bronchi, the end-to-end anastomosis with the trachea is performed.

After complete median sternotomy, the pericardium has to be opened between the superior vena cava and the ascending aorta. The SVC is surrounded by a loop and pulled to the left. The retropericardial portion of the right pulmonary artery is ventrally freed from pericardium and pulled caudally. By pulling the ascending aorta to the right, the tracheal bifurcation can be seen. After transection of pretracheal fascia, infracarinal lymph nodes are now visible. After dissection of this compartment avoiding radical devascularization, trachea and the main stem bronchi are exposed and the level of transection is defined. The proximity of the laryngeal recurrent nerve has to be kept in mind.

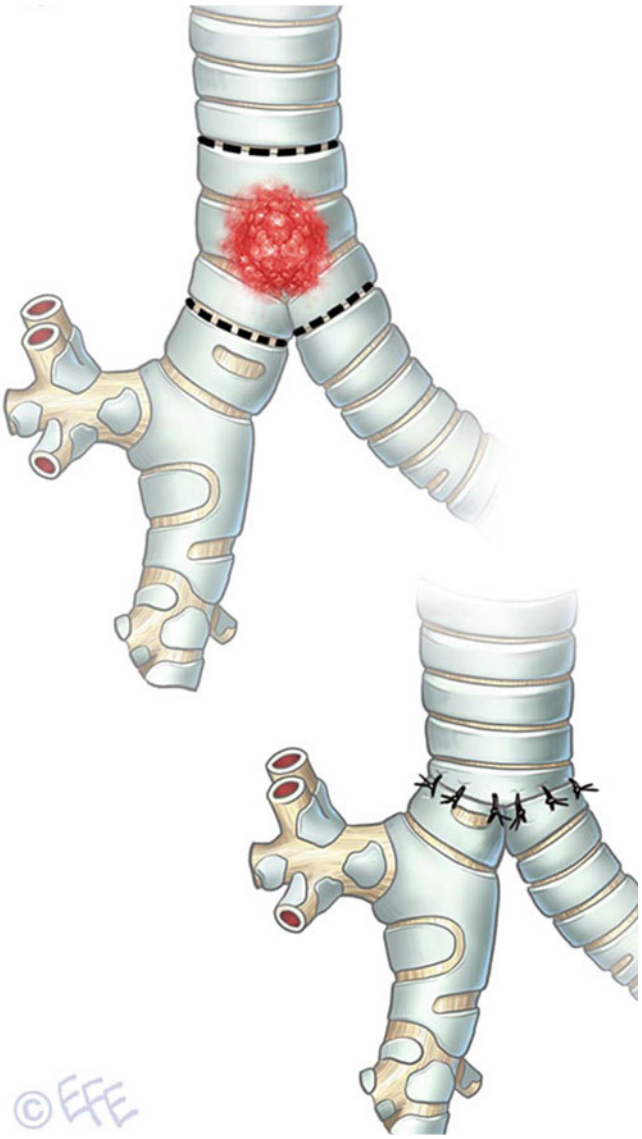

Fig. 47.5 Tumor involving the carina. Principle of reconstruction (Reprinted with permission from Dienemann H et al. editors. Chest surgery Atlas. Springer; 2013.)

Reconstruction starts with a side-to-side suture of the main bronchi with ties placed on the outside. The end-to-end anastomosis with a running suture begins at the posterior wall; however, the adaption is withheld until traction sutures are in place and under tension. The adaption can be supported by additional traction sutures placed more proximally and more distally to the anastomotic level. A flexion of the head can further support adaptation as well. Once the anastomosis is completed, leakage should be excluded by applying positive airway pressure of up to 35 cm H_2O. Pericardial fat flaps are suitable for coverage, as an alternative omentum majus may be used, which are more versatile and can be retrieved using a short extension of the skin incision.

(c) *Carina and Left Main Stem Bronchus* (Fig. 47.7)

Tumorous infiltration of the complete left main stem bronchus simultaneously involving the carina or the distal trachea

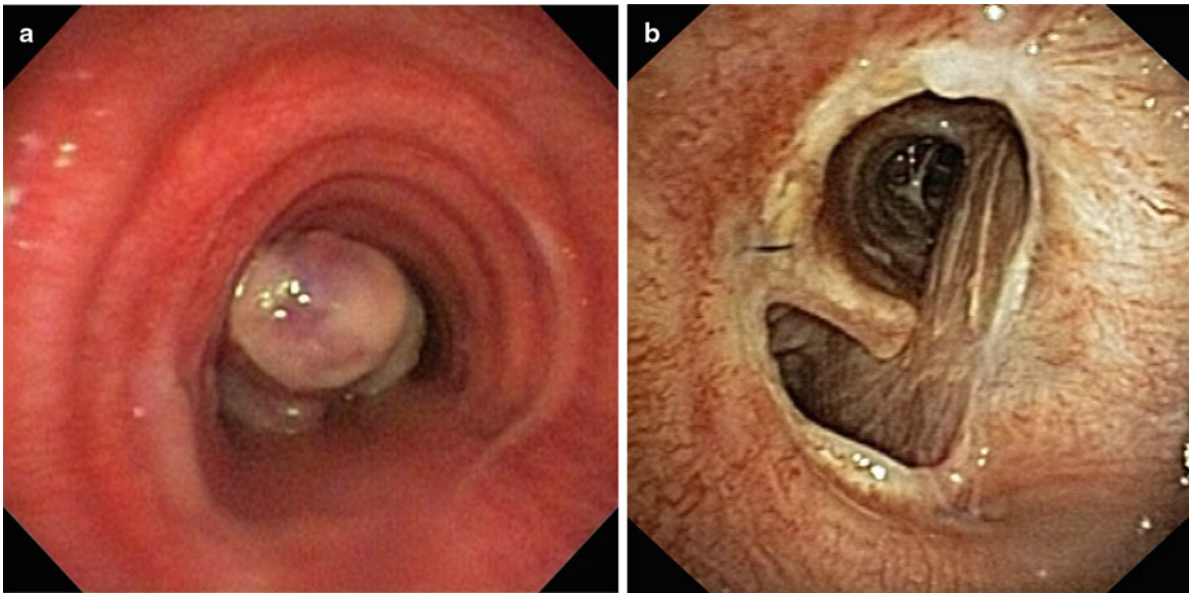

Fig. 47.6 (**a**) Carcinoid tumor, originating from the main carina. (**b**) Endoscopic aspect on day 7: neo-carina created by side-to-side anastomosis of the main stem bronchi; circular end-to-end anastomosis between main bronchi and distal trachea. Uneventful healing

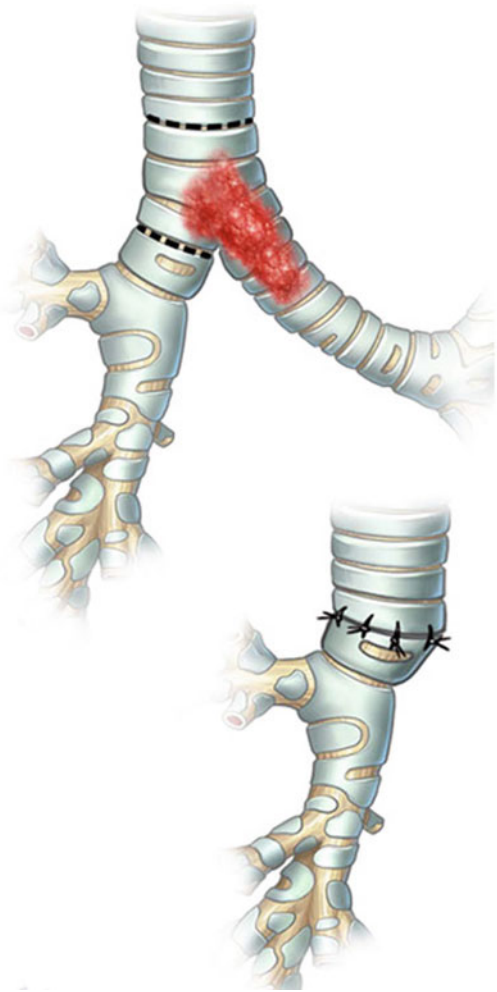

Fig. 47.7 Tumor involving carina and left main stem bronchus. Principle of reconstruction (Reprinted with permission from Dienemann H et al. editors. Chest surgery Atlas. Springer; 2013.)

is quite rare. A left lateral thoracotomy or a hemi-clamshell incision is indicated. For comprehensive exploration of the operative field, intrapericardial inspection and dissection of vessels are often mandatory. The left branch of the pulmonary artery is mobilized down to the bifurcation of the truncus which requires division of the Lig. Botalli under preservation of the N. laryngeus rec. Once the veins and the left pulmonary artery are secured and divided, the tracheal bifurcation is exposed. The aortic arch has to be freed from mediastinal pleura and adhesions before it is surrounded by tapes so that it can be moved back and forth thus improving exposure of the distal trachea. Before the distal trachea and the right bronchus are transected, jet ventilation of the right lung has to be prepared and the ventilation tube has to be retracted up into the upper half of the trachea in order to be able to take advantage of its elastic properties which is a precondition for a traction-free anastomosis. Optimal exposure of the anastomotic area is achieved by cautious rotation of the heart to the right under continuous blood pressure control. After completion of the anastomosis – using techniques as described above – and underwater testing, coverage is recommended using a pericardial fat flap. Closure of the pericardium is mandatory thus to prevent arrhythmias and luxation.

Results

Complicated healing of anastomoses is the strongest predictor of morbidity and mortality. Risks are increased by tension, long-term positive pressure ventilation, residual tumor in the transection plane, and radical devascularization as a result of lymph node dissection and exposure of the anastomotic region. Ventilation leads to barotrauma of the

anastomosis and promotes bronchopulmonary infection. This in return has a negative impact on the healing process. Therefore, extraordinary diligence in preparation, anastomosing, and coverage is of highest priority.

The length of the defect is proportional to the tension of the anastomosis. Resection of more than 4 cm is regarded as a limit for right-sided sleeve pneumonectomies (the measurement is to be taken before interruption of continuity), since mobilization of the left main stem bronchus is limited due to the aortic arch. Longer distances can be managed if the distal trachea has to be connected with the right main stem bronchus. This requires an extended release maneuver; the left main stem bronchus has to be connected with the intermediate bronchus in an end-to-side fashion.

A simple way to reduce tension on the anastomosis is the ventral flexion of the head, which should be performed in any case and sustained over the first couple of days. In addition, any approach to the chest offers the possibility to bluntly dissect the connective tissue around the trachea and main bronchi. Finally, via the transpleural approach, transection of the ipsilateral Lig. pulmonale and the incision of the pericardium around the lower pulmonary vein is an option. The laryngeal release maneuver has no substantial effect.

Complete resection (R0) is the goal of any tumor operation. In critical cases, a technically difficult anastomosis has to be avoided in favor of an R1 resection. This has to be especially taken into consideration if an adenoid cystic carcinoma is being dealt with, which typically spreads longitudinally in the submucosal layer, while mucous membranes seem to be unaffected.

Postoperative care starts immediately following surgery with endoscopic inspection. Debris and blood clots have to be removed thoroughly; the anastomotic region has to be inspected in order to exclude bleeding and incorrectly placed sutures. Intensive care surveillance over a period of 2–3 days is recommended for monitoring fluid balance, providing immediate bronchoscopy in case of secretion retention, and early diagnosis of cardiac arrhythmias, which are the most common postoperative event after major chest surgery.

A follow-up bronchoscopy to assess anastomotic healing should be carried out at least twice before discharge in order to recognize dehiscence and breakdown as early as possible. These are heralded by necrosis of mucous membranes, ulcerations, hemoptysis, and foetor. Sufficient buttressing may prevent fistulation or a complete breakdown. In case of imminent or existing dehiscence, surgical intervention must be undertaken to prevent arrosion of a major vessel. Most often, stenting is not able to achieve the complete sealing of a leakage and is therefore only recommended in cases with high risk of aspiration. Stenting should not be regarded as a permanent solution.

If mediastinal radiation therapy due to extended disease is indicated (N2, R1/R2 resection), it may not be started within 3 weeks following surgery. In any case, a complete healing of the anastomosis needs to be confirmed. According to recent literature, the operation mortality of the resection of the bifurcation is less than 10%; the 5-year survival rate of patients with lung cancer (N0/N1) is reported to be at 40%.

Suggested Reading

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Techniques for Laryngotracheal Reconstruction

48

Ramon Franco Jr.

The upper airway (larynx and trachea) is more than just a passive conduit for the passage of air necessary for life. The densely innervated larynx with its extremely fine control over numerous muscles is responsible for the protection of the lower airway during swallowing through its sphincteric contraction, is supremely important in the generation of cough to expel offending materials from the trachea, and automatically adjusts its aperture to vary airway resistance. A fortunate by-product of its sphincteric action is the well-known ability to produce voice, the result of coordination between proper subglottal air pressure, closely approximated vocal folds, and entrained oscillation of the pliable vocal fold mucosa.

The ability to deliver oxygen to the lungs and transport carbon dioxide out of the body is hampered by a decrease in the cross-sectional diameter of the larynx and trachea. In the adult, the level of the glottis is the narrowest cross-sectional diameter of the upper airway, while the narrowest part in a newborn is the subglottic larynx. There are morphometric gender differences with males possessing longer and wider larynges and tracheas than women (Table 48.1).

Airway Assessment, Grading Systems, and Symptoms of Airway Stenosis

It is important to ascertain the level of the stenosis within the airway, whether it is a solitary lesion or multifocal, the length of the stenosis and how narrow it becomes. Computed tomography is the mainstay of imaging to visualize the upper airway and offers the surgeon a "road map" to assess the entire upper airway. Specifically, CT allows for objective and quantifiable assessment of the length and diameter of the stenosis and the normal caliber of the airway. CT data can be reformatted into coronal sections and 3-D reconstruction (Fig. 48.1) of the airway to reveal a cast of the airway to aid in the visualization of the narrowing and its relationship with surrounding structures. Due to the relatively long acquisition times, MRI images can be blurry due to the movement of the trachea from breathing and the beating of the heart. Because of this, MRI is not as well suited to visualizing the airway compared to CT.

The gold standard in evaluating laryngotracheal stenosis continues to be direct visualization in the operating room under general anesthesia. Assuming the patient is able to breathe on his/her own prior to surgery, the patient can be given oxygen by mask while using IV agents to achieve anesthesia. The airway can be controlled using a laryngeal mask airway if difficulties arise so as not to disturb the laryngeal or tracheal airway. The larynx is then suspended to allow bimanual examination and manipulation of the airway. Jet ventilation is the preferred method because it does not cannulate the airway leading to artificial changes one can get with intubation (laryngeal or tracheal injuries with bleeding, dilation of the stenosis leading to artificially enlarged stenoses). If endotracheal intubation is performed, the endotracheal tube is removed each time the airway is to be examined and promptly replaced as the oxygen saturation begins to decline.

A 0-degree Hopkins rod is introduced down the barrel of the laryngoscope and is used to visualize the airway lumen via a video monitor. The video system allows the members of the airway team to see the endoscopic examination in real time and captures video for review after the procedure (Fig. 48.2). Structures and landmarks can be measured using the Hopkins rod by marking the barrel of the Hopkins rod with tape at the upper incisors when the tip is at the level of the glottis, lower border of the cricoid, and the upper and lower parts of the stenosis. This allows for accurate measurements of the length of stenosis that can be correlated with the

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Table 48.1 Gender differences in tracheal measurements

Tracheal measurement	Males ($n=40$)	Females ($n=20$)	All ($n=60$)	Males versus females statistics
Length (mm)				Difference between means 6.8
Mean ± standard deviation	105.1 ± 9.8	98.3 ± 8.7	102.8 ± 9.9	95% CI 1.6–11.9
Range	86.1–123.9	78.8–123.0	78.8–123.9	$P=0.01$
Maximum antero-posterior diameter (mm)				Difference between means 3.4
Mean ± standard deviation	22.6 ± 2.9	19.2 ± 2.6	21.4 ± 3.2	95% CI 1.9–4.9
Range	16.8–28.6	12.7–23.8	12.7–28.6	$P<0.0001$
Maximum transverse diameter (mm)				Difference between means 4.2
Mean ± standard deviation	27.1 ± 3.4	22.9 ± 2.6	25.7 ± 3.7	95% CI 2.5–5.9
Range	20.1–34.5	17.3–27.8	17.3–34.5	$P<0.0001$
Estimated volume (cm^3)				Difference between means 10.8
Mean ± standard deviation	35.6 ± 6.8	24.7 ± 6.1	32.0 ± 8.3	95% CI 7.2–14.4
Range	18.9–53.6	12.9–35.7	12.9–53.6	$P<0.0001$
Subcarinal angle of bifurcation (°)				
Mean ± standard deviation	76 ± 20	81 ± 20	78 ± 20	95% CI −15.2 to 6.3
Range	36–121	47–115	36–121	$P=0.41$

From Kamel et al. In vivo and in vitro morphometry of the human trachea. Clin Anat. 2009;22:571–79

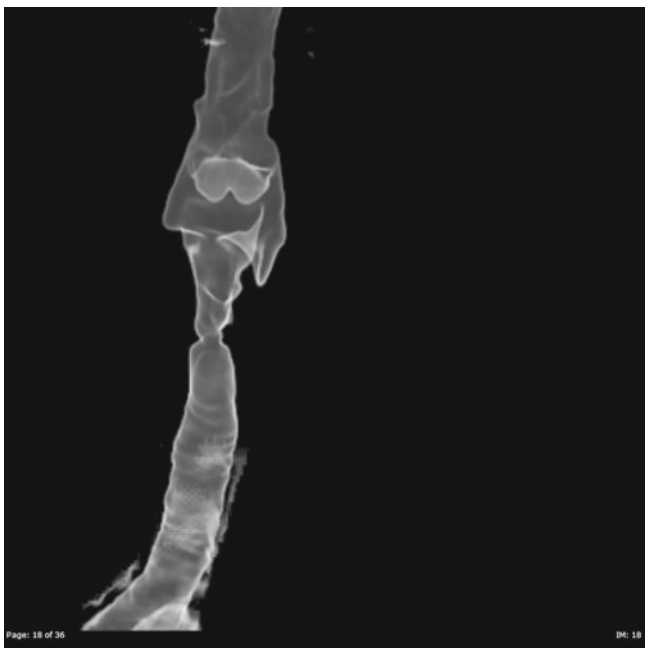

Fig. 48.1 3-D reconstruction of airway. Axial CT data is carefully reconstructed into this three-dimensional image that can be rotated and manipulated. The area of stenosis can be clearly defined in this image

CT data. The amount of narrowing within the airway can be described using several popular grading systems such as the Cotton-Myer or McCaffrey (Tables 48.2 and 48.3) that assess the percentage of the airway that remains compared to the normal caliber. These systems lack accuracy, lumping patients with a broad range of stenoses into the same category (as in grade I Myer-Cotton with a 0–50% narrowing) because functionally they behave similarly. The size of stenosis can be accurately measured by introducing instruments of known diameter and passing them through the area of stenosis.

The airway can be assessed in the awake-clinic setting with flexible nasolaryngoscopes or bronchoscopes to immediately gain an understanding of the magnitude of the airway stenosis. This is ideal for patients who wish to avoid a diagnostic procedure in the operating room or for those who are too medically unstable to safely undergo a diagnostic procedure under general anesthesia. This method requires only topical application of a local anesthetic with a video system to visualize and record the examination. Our preferred method is to spray 2% lidocaine with 0.025% oxymetazoline into the nasal cavities bilaterally followed by a transtracheal injection of 2 cc of 4% lidocaine. The flexible scope is introduced down to the level of the mainstem bronchi/carina and pulled back out of the airway. In a fashion similar to that previously described for marking distances using a rigid Hopkins rod, starting from distal to proximal, the flexible scope can be marked to represent the distal and proximal edges of the stenosis and the level of the vocal folds.

The biggest advantage of direct airway visualization is the ability to palpate and manipulate the airway and alter the stenosis using rigid instruments, balloons, lasers, or medications that can be applied or injected at the time of the endoscopy to alleviate the effects of the stenosis. We will discuss the specifics of these treatments later in this chapter.

The most common symptoms of upper airway stenosis, including dysphonia, dyspnea, cough, and stridor, occur after stenosis reaches a critical narrowing to induce these symptoms. At the point of narrowing in the airway, the resistance to airflow is inversely proportional to the fourth power of the radius at the stenosis and directly proportional to the length of the stenosis. As the resistance increases, the patient has to work harder to move air through the constricted segment

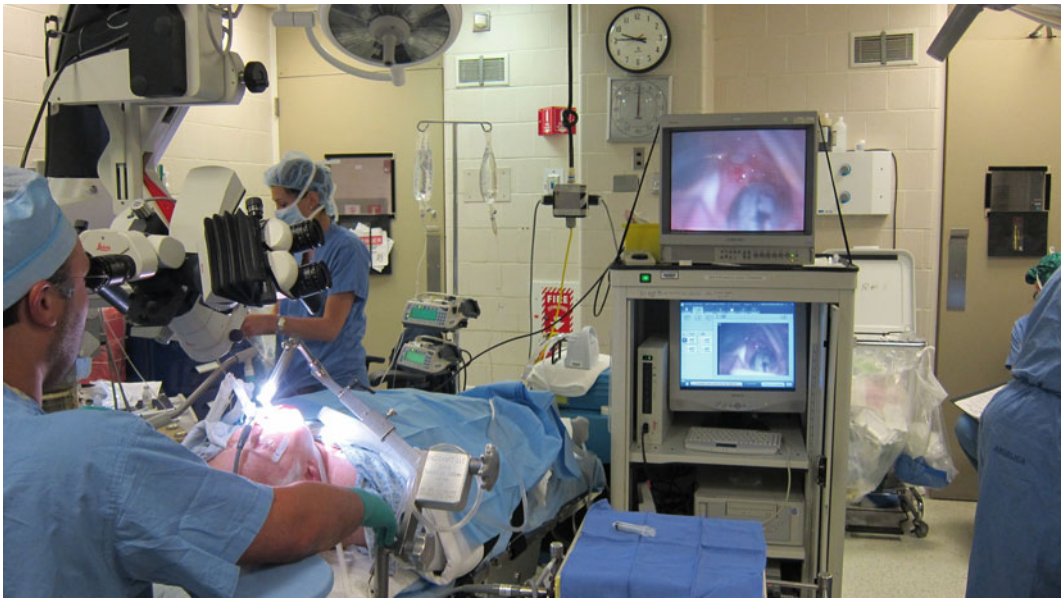

Fig. 48.2 Videoendoscopic tower. The videoendoscopic tower allows the surgical team to visualize the stenosis and capture video and still images that can be reviewed in the OR or clinic to facilitate patient education, assess response to intervention, or plan future interventions

Table 48.2 Myer–Cotton grading scale

Grade I	Up to 50% obstruction
Grade II	51–70% obstruction
Grade III	Above 70% with any detectable lumen
Grade IV	No lumen

Adapted from Meyer et al. Proposed grading system for subglottic stenosis based on endotracheal tube sizes. Ann Otol Laryngol. 1994;103 (4 Pt 1):319–23

Table 48.3 McCaffrey classification

Stage I	Lesions confined to the subglottis or trachea and are less than 1 cm long
Stage II	Lesions are isolated to the subglottis and are greater than 1 cm long
Stage III	Subglottic/tracheal lesions not involving the glottis
Stage IV	Lesions involve the glottis

McCaffrey TV. Classification of laryngotracheal stenosis. Laryngoscope. 1992;102 (12 Pt 1):1335–40

giving the patient dyspnea that begins with heavy activity (running, swimming, climbing) and progresses to dyspnea at rest in highly critical stenosis. Turbulent airflow leads to the airway noise we call stridor and alters the way the air hits the vocal folds, leading to a weak and hoarse voice. The brassy cough is due to the altered mucociliary clearance at the stenosis that causes accumulation of mucus at the undersurface of the stenosis and encroaches on the airway requiring coughing to blow this mucus past the stenosis in order to relieve this dynamic narrowing. It is important to realize that as the airway becomes more narrow, minor changes result in much greater symptoms (i.e., the change from 7 to 6 mm results in much greater symptoms compared to the change from 13 to 12 mm).

Etiologies

In the modern industrialized world, laryngotracheal stenosis is mainly an iatrogenic condition, the end process of airway damage from endotracheal intubation. It is estimated that anywhere from 0.9% to 8% of intubations lead to some form of identifiable long-term sequelae. Factors that are important to the development of laryngotracheal stenosis include prolonged intubation (as in the ICU setting for greater than 1 week), traumatic intubation with disruption of the laryngotracheal mucosa, intubation with too large a tube or with too small a tube where the balloon pressures required to maintain a seal cause mucosal ischemia, or movement of the tube due to swallowing or repeated neck flexion and extension. ICU patients are more susceptible in a multifactorial way with the interplay of the underlying medical condition, reduced ability to heal, and the bathing of the airway in a combination of gastric and oral secretions due to altered sensation and altered consciousness.

In the minority of patients, laryngotracheal stenosis is not the result of intubation injuries. Because there are conditions where we can intervene and halt the process of stenosis, it is important to mention them. Inflammatory or immune system problems such as Wegener's granulomatosis, sarcoidosis, pemphigoid, and amyloidosis can present with airway

narrowing, and each has a different management scheme that should be followed. Other causes include airway tumors, the sequelae from direct damage from surgical procedures meant to deal with other distinct problems, and tracheostomy tubes inadvertently placed through the cricothyroid space (intralaryngeal placement) instead of into the trachea.

There is a group of patients who have a presentation that is, as of yet, considered to be idiopathic. These patients are almost exclusively female, tend to present at a moderately early age (40s to 60s), and do not have a history of intubation within several years of the onset of symptoms. In some cases, there is no history of intubation. It is important to respect our ignorance in understanding the etiology of their stenosis and resist overly aggressive treatment that may leave them with severe postsurgical changes to the voice and persistent disease.

Laryngopharyngeal reflux has been identified as a cofactor in stimulating and promoting the formation of laryngotracheal stenosis. Stomach acid and enzymes (pepsin) make their way up the esophagus, and microaspiration events during silent reflux introduce small quantities of these caustics materials into the upper airway causing inflammation and an environment conducive to an exaggerated healing response after minor airway mucosal disruption. LPR alone cannot account for the episodes of idiopathic subglottic stenosis since men and women both are known to reflux but only women present with idiopathic subglottic stenosis.

Surgical Treatment

Treatment of laryngotracheal stenosis is highly dependent on the particulars of the etiology. Although the vast majority of cases are related to a clear-cut history of intubation injury, care must be taken to rule out the less common but potentially medically treatable and potentially fatal disorders such as Wegener's granulomatosis. This chapter will focus on the surgical management of laryngotracheal stenosis.

Surgical treatments can be divided into endoscopic and open interventions, each possessing inherent advantages and disadvantages that we will discuss. It is important to realize that the choice of an endoscopic or open procedure should be made after synthesizing all of the available patient data and formulating a plan to treat the patient symptoms in partnership with the patient. The designation "endoscopic" or "open" defines an approach but tells us nothing about the actual procedures to be performed. Endoscopic approaches can be further subdivided into procedures that can be performed with the patient awake in the clinic setting or those performed in the operating room. With few exceptions, open procedures are performed in the operating room under general anesthesia (the major exception being tracheotomy that can be performed at the bedside under straight local anesthesia).

Endoscopic Approaches for Diagnosis and Treatment

Although the initial in-office examination typically includes an endoscopic examination using a flexible nasolaryngoscope that is used to assess laryngeal function and visualize the subglottic larynx and the trachea, the traditional endoscopic procedures are performed in the operating room under general anesthesia with highly variable techniques of ventilation due to institutional/surgeon/anesthesia personnel preference ranging from jet ventilation, endotracheal intubation, use of a laryngeal mask airway (LMA) to apneic techniques. Techniques that do not require intubation of the stenotic area such as jet ventilation or the apneic method do not disrupt the airway mucosa since a large tube is not introduced through the stenosis. This allows for an accurate assessment of the nature of the stenosis. Intubation many times alters the airway by introducing bleeding and dilating the stenosis as the tube pushes past. The largest direct laryngoscope that will fit into the laryngeal introitus should be used as the larger size offers more room to introduce and manipulate instruments. A video system with a 0-degree Hopkins rod will allow visualization of the airway and a way to accurately measure the length and location of the stenosis. The stenosis can be palpated to determine how fibrotic it is. All of this information should be recorded in a systematic fashion and will be used to formulate appropriate treatment options.

After a thorough visual investigation of the airway, biopsies can be sent to exclude other causes of stenosis including tumors, vasculitis, infection, and malignancy. At this time, even if the plan is to eventually perform a definitive procedure, the airway can be dilated to give the patient temporary relief from the effects of the stenosis. There are a variety of instruments to dilate the stenosis ranging from rigid to semirigid dilators that (Fig. 48.3) require passing progressively larger instruments into the stenotic segment to balloon dilators. Because balloons exert force in a radial manner, they exert their force directly on the stenosis, uniformly dilating without the associated collateral mucosal airway damage associated with introducing and removing multiple dilators. Balloons for airway dilation currently can be found in sizes ranging from 5 to about 20 mm (Fig. 48.4).

The stenosis can be disrupted using "cold" microsurgical instruments such as scissors or forceps if the stenosis is mainly within the subglottis or upper trachea. More distal tracheal stenoses are not as amenable to this technique due to the limitations of the length of the instruments and visualization of the lesion with the instruments occupying space within the barrel of the laryngoscope and the lumen of the airway. It is important to not create circumferential wounds within the airway as there will be circumferential stenosis during wound healing. Partial resection of scar tissue can be

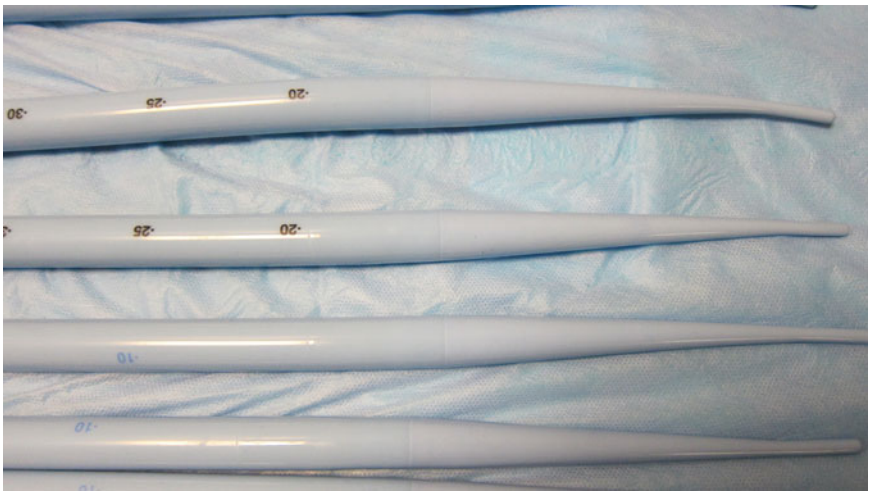

Fig. 48.3 Dilators. Dilators are tapered to allow insertion into the stenotic segment. Progressively larger dilators are inserted until resistance is met. This gradually opens the airway. This technique is thought to cause both longitudinal and radial trauma to the airway. These dilators are typically used for firm stenoses

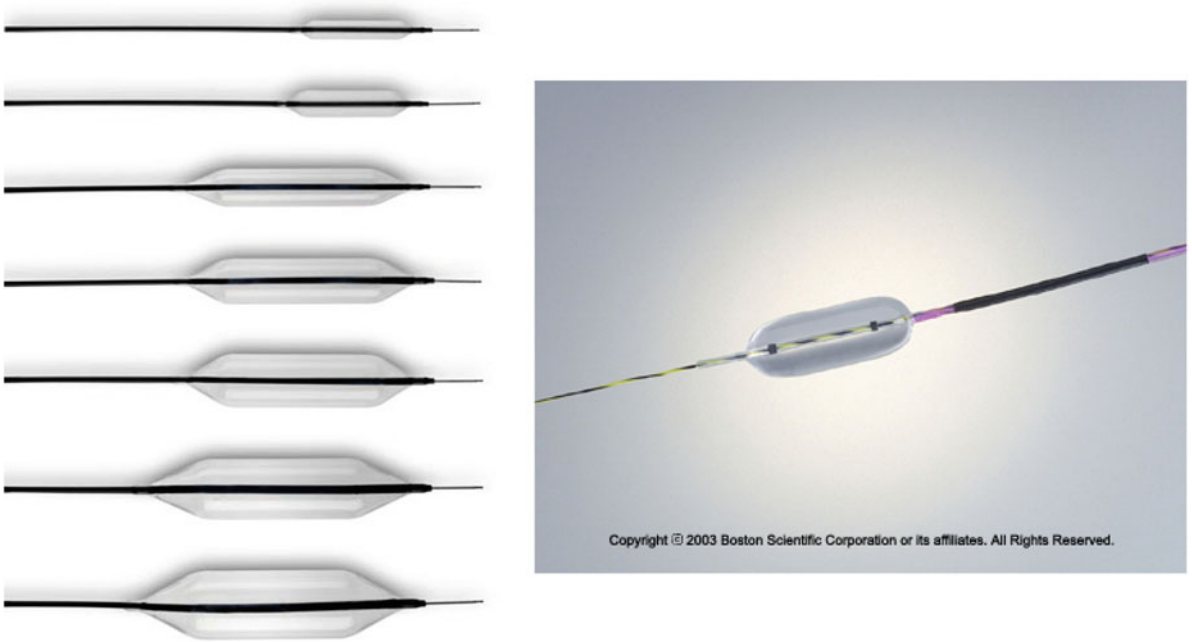

Fig. 48.4 Airway balloons. Airway balloons are thought to cause radial trauma by expansion and do not to cause trauma to the stenotic segment or airway walls as they are inserted collapsed into and out of the airway. A variety of sizes and lengths are available ranging from 5 to 20 mm. Acclarent Inc. (Menlo Park, CA) and Boston Scientific (Natick, MA) both manufacture balloons for airway dilation (*Images were accessed from the Acclarent website* http://www.acclarent.com/solutions/airway-stenosis/inspira-air/ *and Boston Scientific* http://www.bostonscientific.com/Device.bsci?page=HCP_Overview&navRelId=1000.1003&method=DevDetailHCP&id=10005331&pageDisclaimer=Disclaimer.ProductPage)

performed within each quadrant, making sure to preserve intervening "normal"-appearing mucosa.

The carbon dioxide laser (CO_2) is a tool that allows the surgeon to cut through tissue with minimal bleeding. The CO_2 laser delivers light at 10,600 nm, a frequency that is absorbed by water in the tissues. The CO_2 laser should be used in a super-pulse repeat or in true pulsed mode to create linear incisions and vaporize a sliver of scar in each quadrant while minimizing thermal damage to the surrounding tissue. Since the CO_2 laser can be directed from a distance via a micromanipulator mounted on the operating room microscope and has an associated aiming beam, it can be used to open stenotic areas not accessible to rigid instruments introduced via the mouth (Fig. 48.5). The CO_2 laser energy can

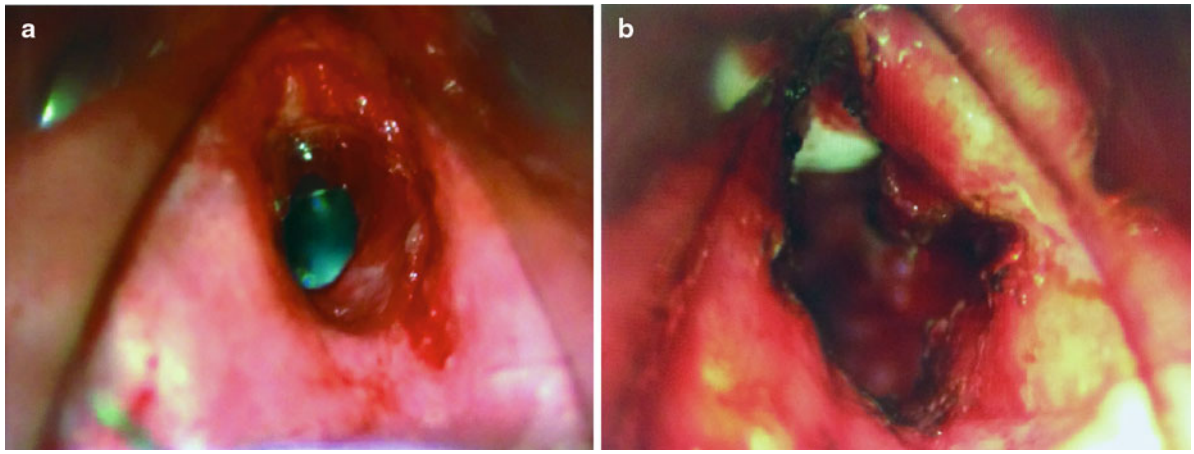

Fig. 48.5 Endoscopic scoring of the subglottic stenosis with the CO_2 laser. A cruciate incision prevents circumferential de-epithelialization and minimizes collateral thermal damage while opening the airway. The idea is to prevent a circular wound which will once again narrow the airway as healing occurs. (**a**) Is the stenosis prior to intervention. (**b**) Post-CO_2 laser treatment. Note the cruciate incision made with the CO_2 laser. This image is prior to balloon dilation of the stenosis

also be delivered through a fiber within the working channel of a flexible nasolaryngoscope or bronchoscope passed through the laryngoscope to achieve visualization and control the CO_2 laser in the treatment of distal lesions. Regardless of whether cold instruments or lasers are used, endoscopic resection of scar has a diminishing success rate as the length of stenosis increases. Stenoses longer than 1.5 cm have very high rates of restenosis when performed as a single endoscopic procedure – most surgeons advocate for an open procedure when there is long-segment disease (>1.5 cm).

Adjuvant treatment at the time of endoscopic dilation includes injection of steroids (4 to 8 mg of Decadron, 4 mg/cc) into the area of stenosis if there appears to be inflammation within the stenosis. Mitomycin-c is derived from the bacterium *Streptomyces caespitosus* and has the ability to retard the healing (scarring) process by inhibiting fibroblasts from making collagen. Mitomycin-c also delays reepithelialization where it is applied. Mitomycin-c in concentrations of 0.4 mg/cc to 2 mg/cc can be applied with neuro-pledgettes to areas that have undergone partial resection using cold instruments or the CO_2 laser and appears to have more efficacy when applied several times over the course of a few weeks rather than once. It is important to note that the optimal treatment interval and dosage have not yet been defined.

Awake-Endoscopic Treatment

The widespread availability of flexible channeled scopes for use in the upper airway has expanded the possibilities of what can be performed in the outpatient-awake (clinic) setting to include nearly anything that can be performed endoscopically in the operating room. By expanding what is done during the initial diagnostic session in the clinic, the physician can thoroughly inspect the airway and turn the encounter into a therapeutic session through the use of balloon dilators, lasers, grasping instruments for biopsy, and injection of steroids into the stenosis. There are several advantages to the patient, physician, and overall healthcare system to performing the intervention in the awake-outpatient clinic setting. Because the patient is not exposed to general anesthesia, there is no risk of liver failure, kidney failure, myocardial depression or infarction, cerebrovascular accident, or the other potential consequences of general anesthesia. Patients with multiple medical conditions who are normally considered poor surgical candidates can safely have relief from their dyspnea by undergoing a procedure in the awake setting. Patients are able to drive themselves to the office and back home because the procedure is performed under straight local anesthesia. The physician will find the advantages which include being able to assess the airway in its natural state with the ability to see where there is collapse because the patient is awake and spontaneously ventilating, the ability to ask the patient to perform tasks such as panting or coughing, no lost time between diagnosis and initial treatment, a substantial decrease in the time between scheduled procedures compared to the operating room, less time per procedure, and having happier patients who are appreciative and feel you, their physician, are responsive to their needs. The system overall derives substantial cost savings since there is no need for the added costs of anesthesia, the operating room, or the postoperative care normally associated with interventions in the operating room.

Anesthesia for Local Awake Procedures

Although one loses the ability to perform bimanual manipulation when using a flexible scope in the clinic, there is virtually no loss in visualization because the optical resolution is excellent for the new distal-chip CCD (charge-coupled devices) scopes. A mixture of 2% lidocaine with 0.025% oxymetazoline is sprayed into the nasal cavities followed by a transtracheal injection of 2 ml of 4% lidocaine. The trachea is grasped between the thumb and index finger, and the needle (23- or 25-gauge 1.5-in. (3.8-cm) needle) is placed in the midline at the level of the first or second tracheal ring. Depending on the level of obstruction, the needle can be inserted into the thyrohyoid or cricothyroid space above or below the level of stenosis. To confirm the needle tip is in the airway, air is aspirated into the syringe. The lidocaine is then delivered as quickly as possible causing the patient to cough. The patient should be given tissue paper and asked to cover the mouth prior to the injection since the presence of the lidocaine in the airway should stimulate a fairly aggressive cough (Fig. 48.6). Confirmation of proper placement of the lidocaine is the presence of a "wet" cough and the patient acknowledging the taste of lidocaine. Care must be taken to ensure the needle is both in the midline and not pushed in deep so that the tip is within the posterior tracheal wall/esophagus. A posterior and lateral placement of the needle tip can result in a temporary unilateral (ipsilateral) vocal fold paresis from infiltrating the recurrent laryngeal nerve with lidocaine. Injection of the posterior tracheal wall can result in either dysphagia or worsening dyspnea through further narrowing of the airway. The airway from the larynx to carina will be ready for examination within a minute of the injection.

It is important to warn patients to refrain from eating or drinking for at least one hour after the injection as the anesthesia is profound and places them at risk for aspiration while abolishing their natural protective cough reflex. Prior to injection, the medical practitioner should explain that due to a lack of sensation after the injection, it can be normal to feel as if there is a problem with breathing or swallowing. This is due to the lack of sensing the air flowing through the larynx and liquids within the laryngopharynx and esophagus and is expected to return to normal after the anesthesia wears off.

After introducing a channeled flexible nasolaryngoscope into the nose, the airway is assessed from the nasopharynx to the carina. The flexible, fiber-based lasers such as the 585-nm pulsed dye, 532-nm pulsed KTP, or even the CO_2 laser can be introduced through the working channel to photocoagulate or ablate tissue. The CO_2 laser can be used to create radial incisions in the stenosis with minimal bleeding. Tissue can be manipulated through the use of the endoforceps introduced through the working channel, and pieces can be removed and sent to pathology for histological analysis. Steroids can be injected into the stenotic region alone or in conjunction with laser ablation or dilation.

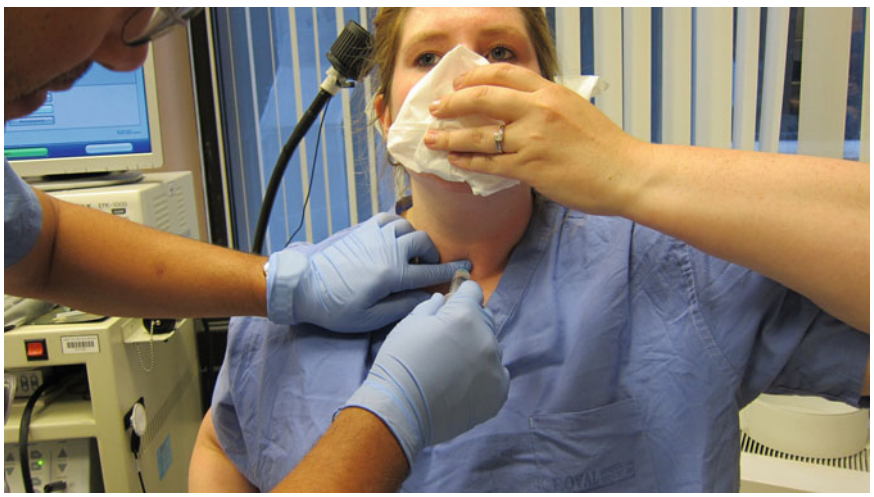

Fig. 48.6 Transtracheal lidocaine for office-based assessment and treatment for subglottic stenosis. The trachea and larynx (cricoid cartilage) are palpated while the needle (23- or 25-gauge 1.0- to 1.5-in. needle) is placed in the midline at the level of the first tracheal interspace. Depending on the level of obstruction, the needle can be inserted below this level. To confirm the needle tip is in the airway, air is aspirated into the syringe. Two milliliters of 4% lidocaine is then delivered as quickly as possible into the trachea causing the patient to cough and anesthetize the trachea and larynx. The patient should be given tissue paper and asked to cover the mouth prior to the injection since the presence of the lidocaine in the airway will stimulate a fairly aggressive cough

Awake Balloon Dilation

Balloon dilation is possible in the awake-clinic setting without the use of sedation. Topical airway anesthesia is administered as described above. All instruments and tools (nasolaryngoscope, balloon, guidewire, etc.) should be assembled and be ready for use prior to administration of the tracheal lidocaine to optimize the time the patients are comfortably anesthetized (about 10–15 min). Awake balloon dilation is a multistep process that begins with determining the nostril the patient breathes through better as this will be the side the balloon is passed down. The channeled nasolaryngoscope is passed through this "larger" side and is held just above the level of the false vocal folds while a guidewire is pushed down the working channel until it is seen protruding from the tip. The nasolaryngoscope with guidewire is advanced through the vocal folds into the subglottis until just above the stenosis to allow advancement of the guidewire distal to the stenosis. While the scope is being retracted from the upper airway, the assistant controls the guidewire, keeping its position constant by making sure to keep pace with the retracting scope. When the scope has been completely pulled out of the nose, the assistant will hold the guidewire at the nasal tip while the nasolaryngoscope is introduced into the opposite nostril and advanced to afford a view of the guidewire entering the larynx. The balloon dilator is placed over the guidewire and carefully passed through the nasal cavity and nasopharynx (while controlling the position of the guidewire) until it is seen just above the larynx. The balloon and nasolaryngoscope are advanced so the central part of the balloon is placed at the level of the stenosis, and it is inflated to the recommended pressure. The patient is asked to hold his/her breath during the 5–10 s it takes to inflate the balloon with water and then deflate the balloon. The balloon retains some volume and needs to be pulled up in order to allow the patient to breathe well. It also allows visual inspection of the effects of the dilation. A second inflation of the balloon can be performed prior to slowly and carefully removing the guidewire and deflated balloon as a unit. There is typically a small amount of self-limited bleeding from the dilation process at the stenosis that does not require intervention. Several good coughs will clear most of the blood, or suction can be used through the scope to remove it from the airway. Endoscopic needles (23 or 25 gauge) can be used to deliver steroids into the newly dilated stenosis prior to removing the nasolaryngoscope. Most patients do not require more than 5–10 min of observation after the procedure, and all report instant improvement in their ability to breathe.

Open Surgical Treatments

Tracheotomy

Tracheotomy is the least invasive procedure that can reliably relieve dyspnea through a simple bypass of the stenosis. Because the technique for tracheotomy is well described, we will not go into great detail regarding the steps. Briefly, the neck is palpated to establish the major landmarks consisting of the thyroid notch, the cricothyroid membrane, the cricoid, the trachea, and the midline. A horizontal or vertical incision is made over the trachea below the level of the stenosis, and dissection is carried down to the trachea where an incision is made into the airway to accommodate a tracheostomy tube of appropriate size for the patient. This procedure can be performed under straight local anesthesia or under general anesthesia in a variety of situations and locations (in the intensive care unit, the operating room, surgery center, as an open procedure, or percutaneously) making it truly a very versatile intervention.

Proper placement of the cannula is vital to a successful outcome. The surgeon must be certain that the area of stenosis is above the site of the tracheotomy or it can fail to relieve the patient's symptoms. Because of this, tracheotomy is appropriate for very high stenoses (glottic, subglottic, very high tracheal) and can be used for short- and long-segment stenoses alike. Tracheotomy is not a perfect solution because it does nothing to treat the stenosis. It is simply a bypass of the problem area. Many patients are resistant to tracheotomy due to the cosmetic effects of a cannula in the anterior neck with the associated scar and the extra hygienic care necessary to keep the neck clean. If there is substantial stenosis, tracheotomy will not improve voice since there will still be reduced airflow to the vocal folds. Because the tracheotomy tube anchors the trachea to the skin, the larynx sometimes cannot elevate sufficiently during swallowing increasing dysphagia and possibly increasing the risk of aspiration. Tracheotomy use has its associated risks of fatal airway compromise through mucus plugging because the upper airway is bypassed and low-humidification air is drawn into the trachea. Normally, air is humidified well beyond the level found in ambient air through contact with the mucous membranes of the turbinates in the nose, delivering well-humidified air to the upper airway. The use of an inner cannula, frequent saline irrigation, and humidification is recommended for several months (depends on the local climate – the lower the ambient humidity, the longer it will take) until the patient reaches a state of homeostasis with the production of secretions. A heat and moisture exchanger (HME) is a device that is worn at the tip of the tracheostomy tube and should be

recommended to maintain high tracheal humidification and lower the formation of crusts within the cannula and airway.

The tracheostomy tube can induce the formation of granulation tissue (typically in a suprastomal position), but the tube tip can also cause injury leading to granulation tissue and eventually stenosis distal to the original area of stenosis. There can be displacement of the cannula or weakening of the integrity of the anterior trachea from removing anterior tracheal rings making decannulation in the future difficult without a separate anterior tracheal reconstructive procedure.

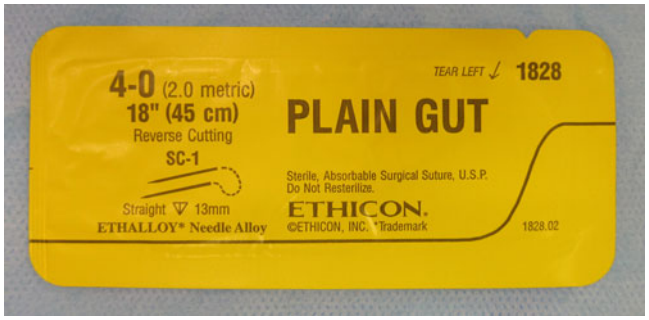

Fig. 48.7 4-0 plain gut suture packet. The suture has needles (SC-1) at both ends that are cut off and used to impale the cartilage graft

Airway Stenting

A more aggressive procedure than tracheotomy is to combine a resection of endoluminal scar with stenting of the airway. This stenting can be short term (6–10 weeks) or long term, and the stents can be anything from completely endoluminal to T-tubes. Endoluminal stents are frowned upon for long-term use due to the problems of tracheal erosion and migration but can be an ideal solution for spanning an area of trachea that has been denuded after resecting scar. The stent can hold a buccal mucosal graft in place for 3–6 weeks followed by endoscopic removal. Endoluminal stents can be considered for those who have a shortened life expectancy due to malignancy or chronic end-stage disease where a large surgery to correct the airway problem is contraindicated.

Stents can also span the area of stenosis in someone who has undergone multiple unsuccessful procedures due to re-scarring with the use of a T-tube. The T-tube maintains airway integrity while also introducing an element of safety with an external limb that allows for suctioning and can act as an accessory airway. When a T-tube is in place, it should be cared for in a similar fashion to a tracheostomy tube (aggressive saline irrigation, local wound care) with the exception that whenever possible, a T-tube should be capped to maintain high airway humidity and minimize crusting. In those whom this is not possible, a humidification cap (HME) should be worn as often as possible.

Laryngotracheal Reconstruction (LTR)

Laryngotracheal reconstruction is a technique where the cartilaginous framework of the larynx is manipulated to allow for expansion in cases of subglottic stenosis. There are several permutations of the LTR procedure, but despite their differences, they share an important common feature – splitting of the cricoid cartilage. Since the cricoid is the area of the stenosis and the region that requires expansion, it is either split anteriorly or anteriorly and posteriorly. After splitting the cricoid, either a stent (endoluminal or T-tube) is placed for 6–8 weeks or an interposition rib cartilage or thyroid

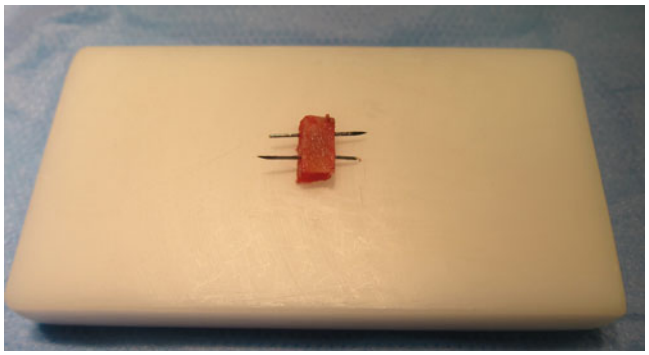

Fig. 48.8 The thyroid cartilage graft is impaled with the reverse-cutting SC-1 needle. The graft can be secured in place without the need for suturing it to the recipient cartilage bed

cartilage graft is placed within the split cricoid to achieve displacement of the cut edges of the cricoid and upper trachea. The perichondrium is left intact on the harvested cartilage while it is fashioned into its final size and shape. Perichondrium should be left on the portion of the graft that is endoluminal to minimize postoperative granulation tissue.

There are different techniques for securing the graft in place. A very popular way of securing the posterior cricoid graft is to create a "boat" shape and wedge the graft between the cut edges of the posterior cricoid with the bulk of the graft posterior to the cricoid and the keel jutting up separating the cut edges. Anterior grafts can be secured via permanent sutures (4-0 monofilament) through the perichondrium and cartilage (in younger patients, the cartilage is soft enough to allow sutures to pass through). Another technique is to skewer the graft with two straight pins so the graft pins impale the edges of the cut cricoid and keep the graft firmly in place without the need for sutures (Fig. 48.7) The straight needles that come on the ends of 4-0 plain gut sutures can be used for this endeavor (Fig. 48.8).

LTRs can be performed as a single-stage procedure or can be staged if a stent is left in place. LTRs also can be performed

with or without performing a tracheotomy at the conclusion of the case.

The success of an LTR is directly dependent on the stage of the stenosis. The chances of failure are highest when the length of stenosis is long and the lumen is narrow. Identifiable traumatic causes for the stenosis such as intubation damage or laceration of the trachea will have a lower failure rate when compared to an idiopathic cause reflecting the biological factors stimulating the stenosis.

Cricotracheal Resection

When the stenotic disease is relatively isolated to the confines of the cricoid without much extension to the vocal folds, a cricotracheal resection (CTR) can be performed to control the disease. The anterior arch of the cricoid is removed along with the endoluminal stenosis leaving the posterior cricoid plate in situ. The cricothyroid muscles are spared by separating them in the midline and shaving them off the arch on a thin base of cartilage anchored laterally to allow for their reapproximation during the reconstructive phase of the surgery. The inferior border of the stenosis is identified by vertically incising the anterior tracheal wall through the stenosis and visually inspecting the interface between diseased and healthy mucosa. The trachea is transected at the appropriate level and will be sutured superiorly to the thyroid cartilage after completely denuding the endoluminal surface of the posterior cricoid. An otologic drill with a diamond burr is very useful in ensuring complete removal of the posterior cricoid mucosa, but any method that can reliably denude the cartilage is acceptable. The posterior tracheal wall is dissected free of the anterior esophageal wall, and limited lateral tracheal dissection (the trachea is nourished via feeding vessels that enter laterally, and the recurrent laryngeal nerves can be found here between the trachea and esophagus), enough to allow the trachea to slide into the resection defect, is performed. Depending on the length of trachea that requires resection, a suprahyoid muscle release can be performed to decrease the tension on the thyro-tracheal anastomosis. The head can also be flexed at this time to aid in reconstructing the airway. Several 2-0 and 3-0 nonabsorbable monofilament sutures are placed from trachea through the inferior thyroid cartilage prior to tying any individual sutures. In case the inferior thyroid cartilage is widely calcified, several small holes can be drilled to allow anchor points where the sutures are passed through to allow strong union between the trachea and thyroid cartilage. Posterior sutures are always tied first, going from midline to lateral. The laterally based cricothyroid muscle flaps are sewn to the midline over the trachea and anastomosis. If so desired, and the specific clinical scenario dictates the need for a tracheostomy tube, this can be placed after the anastomosis is completed when bringing the soft tissues together. A drain is typically placed under the platysma layer. The use of the chin-to-chest suture, or "Grillo stitch," is falling out of favor but can be performed to keep the patient's head in flexion and discourage extension during the first few days.

Postoperatively, the patients are started either on a liquid or a soft-mechanical diet and advanced as tolerated. Patients are placed on antibiotics for 7–14 days (as long as the drain is in place), and an IV/PO steroid taper is given for 7 days. Given the potentially devastating complications of anastomosis dehiscence and subcutaneous emphysema, patients are observed first in an ICU setting and then transferred to airway observation floor care for several days, with the clinical course dictating the speed of progression and eventual discharge. In patients who have very smooth postoperative courses, discharge can occur as soon as 2 days post-op. Patients are routinely sent home with the drain to stay in place for 1–2 weeks to mitigate against having air leaking into the neck and remaining trapped from the thyro-tracheal anastomosis.

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Bronchoscopic Lung Volume Reduction

49

Armin Ernst

Abbreviations

COPD	Chronic obstructive pulmonary disease
NETT	National Emphysema Treatment Trial
SGRQ	St George's Respiratory Questionnaire
VENT	Endobronchial Valve for Emphysema Palliation Trial
CT	Computed tomography
FEV_1	Forced expiratory volume in 1 s

Introduction

Lung volume reduction surgery involves the removal of 20–30% of each lung and targets the most emphysematous segments. Within chronic obstructive pulmonary disease (COPD), patients with heterogeneous upper lobe emphysema and a low-baseline exercise capacity have been identified as a subgroup in whom mortality benefits can be achieved along with improvements in spirometry, exercise capacity, and quality of life. In COPD, both airway narrowing and loss of elastic recoil cause expiratory airflow limitation. During exercise, increasing respiratory rate shortens expiratory time and results in air trapping.

Lung volume reduction corrects loss of elastic recoil by reducing the volume of the most damaged lung segments (dead space) and allowing the remaining less damaged tissues to resize. By eliminating parts of emphysematous lung with the longest expiratory time constants, dynamic air trapping is reduced and exercise capacity can be increased. The operating length of respiratory muscles is also normalized by restoring the normal dimensions of both the chest wall and the diaphragm.

Increased short-term mortality of approximately 5% and postoperative morbidity are the limitations of surgical lung volume reduction. The reported rate of intraoperative complications is 9% and postoperative complications is >50%. Risks include reintubation (21.8%), arrhythmias (18.6%), pneumonia (18.2%), readmission to the intensive care unit (11.7%), and tracheotomy (8.2%). Air leaks with a median 7-day duration have also been reported in 90% of patients. In the National Emphysema Treatment Trial (NETT) study, up to 28% of patients were hospitalized or living in a nursing/rehabilitation facility at 1 month after surgery. Unfortunately, the price of all this morbidity and mortality does not guarantee long-term benefits after surgery. Only 30% of patients in the most favorable subgroup of COPD derived a clinically significant improvement in exercise capacity of >10 W and 48% registered a >8-point decrease in the St George's Respiratory Questionnaire (SGRQ) at 24 months.

The restrictive selection criteria coupled with the relatively high morbidity have been the likely reasons for the decrease in patients undergoing surgical lung volume reduction since the publication of the NETT data. This situation persists in the United States despite established criteria for Medicare coverage and has served as an incentive for the development of less invasive modalities. Bronchoscopic lung volume reduction has pursued various approaches such as blockers, stents, valves, thermal vapor ablation, sealants, and implants. The physiological basis of each modality is not identical and in some cases distinct from even conventional lung volume reduction surgery. The ideal indications also differ with airway bypass stents targeting homogenous emphysema, while valves and thermal vapor ablation target heterogeneous emphysema. Biological sealants and endoscopic coil implants have been used in both homogenous and heterogeneous emphysema.

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Endobronchial Blockers

Endobronchial blockers effect resorption atelectasis by occluding airways leading to emphysematous lung segments. Initially silicone vascular balloons filled with radio-opaque contrast were inserted before the advent of custom-built stainless steel stents with a central occlusive sponge. However, the high rates of endobronchial blocker migration, postobstructive pneumonia, and the need for repeated endoscopic procedures have limited further development or widespread use of this technique.

Endobronchial Valves

Endobronchial valves are the devices studied for the longest and in most patients. It is approved therapy in many countries outside the USA and designed to exclude the worst affected emphysematous regions from ventilation. If segmental or lobar resorption atelectasis can be induced, a physiological effect similar to surgical lung volume reduction can be expected. Therefore, patients with heterogeneous emphysema (which can be upper as well as lower lobe predominant) are ideal candidates for endobronchial valve therapy. Valves allow one-way flow of secretions and air out of an occluded lung segment or lobe during expiration but prevent any distal flow during inspiration. Different endobronchial valve designs are available and being studied: duck-billed (EBV) and umbrella-shaped (IBV) valves.

The EBV valves are supported by a nickel-titanium (nitinol) self-expanding, tubular mesh that is covered with a silicone membrane to form a seal between the valve and the bronchial wall (Fig. 49.1). One-way exit of distal air and mucous is facilitated by the central duckbill. The valves are mounted on to a loading catheter and deployed via the working channel of a flexible bronchoscope. The lobe with the highest heterogeneity score is targeted, and usually 3–5 valves occluding the segments are required (Fig. 49.2). At times, it is possible to seat a single valve into a lobar bronchus. Procedures can be performed under conscious sedation, but it is important to effectively control coughing. Patients with active infections or significant secretions are poor procedure candidates. Deployment involves two stages: An endoscopic measurement gauge is used to size bronchial diameter before a valve of the equivalent size is chosen. The loading catheter with the chosen valve is advanced to the target airway, and the valve is deployed by using an actuation handle. It is crucial to properly size the valves and place them into locations where they are completely occluding, as resorption atelectasis otherwise will likely not occur (Fig. 49.3).

The Endobronchial Valve for Emphysema Palliation Trial (VENT) study was a multicenter, randomized, controlled study that enrolled 220 patients in North America and 111 patients in Europe into the intervention arms. Patients with heterogeneous emphysema as determined by quantitative high-resolution computed tomography (CT) were treated with unilateral therapy targeting lobar exclusion. The North American data showed modest improvements in spirometry and quality of life as measured on the SGRQ at 6 months. The increase in forced expiratory volume in 1 s (FEV_1) was 4.3%, and the difference between the intervention and the control arms was 6.8%. The difference in 6-min walk was 5.8%. Complications were manageable, including COPD exacerbations, pneumothorax, hemoptysis, and pneumonia, and acceptable in rate. There was no procedure-related

Fig. 49.1 Example of a one-way implantable valve (zephyr). The design allows for air and mucous to escape through the valve. The device is placed via a catheter-based system

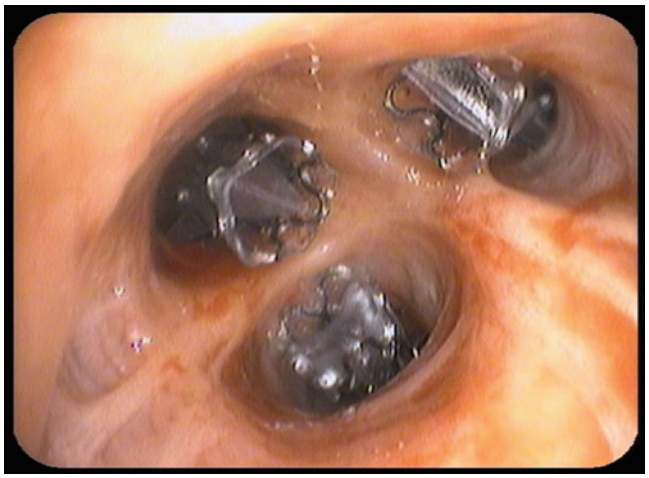

Fig. 49.2 Three valves are placed into the segments of a right upper lobe in a patient with emphysema with the goal to achieve complete occlusion and atelectasis

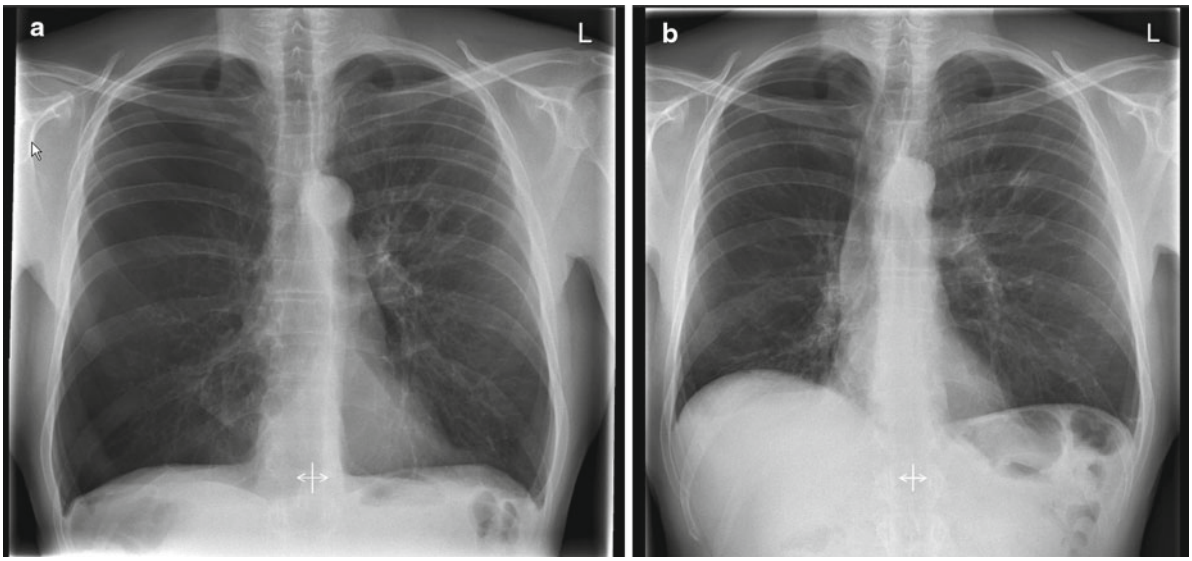

Fig. 49.3 Chest X-ray of the patient shown in Fig. 49.2. The X-ray on the *left* shows the hyperinflated lungs and depressed diaphragm. The X-ray on the *right* demonstrates right upper lobe collapse, volume reduction, and a more normal diaphragm configuration

mortality. Valves were removed during the study in 31 patients for reasons such as valve migration, pneumonia, and COPD exacerbations. Valve removal is generally easily performed with conventional biopsy forceps, and this reversibility presents a major attraction of this technique.

Over 40% of trial sites reported technical error rates of greater than 10% in valve placement, suggesting that technical success cannot be taken for granted. Patients who had evidence of complete interlobar fissures on pre-procedure CT had incremental improvements of forced expiratory volume at 1 s (FEV_1) over those who did not, and the efficacy was further improved in the subgroup of patients who actually achieved lobar isolation.

Using either EBV or IBV valves, lobar atelectasis was not achieved in the majority of patients even with a lobar exclusion approach, whereby all the bronchi to a target lobe were occluded. In the VENT study, only 22% of patients showed complete interlobar fissures and lobar collapse at 1 year. However, the greatest benefits appear to be found in these patients who do develop target lobe atelectasis because of favorable changes in chest wall dimensions.

More limited symptomatic benefits have also been found in a large proportion of COPD patients treated with endobronchial valves despite the absence of any lobar collapse suggesting a role for other physiological mechanisms. It is postulated that by occluding airways, valves increase resistance to airflow such that air is diverted to other relatively less emphysematous parts of the lung resulting in reduced air trapping and dynamic hyperinflation. Moreover, by excluding the most diseased parts of the lung from gas exchange, physiological dead space can be reduced by an interlobar shift of ventilation from the treated lobe to untreated regions of the lung. This is matched by changes in perfusion as a result of hypoxic vasoconstriction and results in better ventilation-perfusion matching in the untreated, more normal lung regions.

Thermal Vapor Ablation

Controlled doses of steam, when delivered to a segmental airway, can produce an inflammatory response that results in lung volume reduction by creating scar formation. The advantage of this technique is that no prosthesis needs to be inserted. The degree of collateral ventilation is also not an issue because the treatment works at the level of the lung parenchyma. Targeting can be staged with several or single segments added in procedures. The energy dose considers the target tissue mass as determined by CT imaging, and a time is calculated to achieve the desired energy delivery. It is therefore crucial to know exactly at which segment or lobe one wants to isolate, as it determines the treatment algorithm based on the dependant lung mass. It appears that 10 cal/kg is the most commonly dose used in current trials. Procedures are currently mainly performed under general anesthesia to completely control cough and balloon placement. A reusable 2-mm vapor catheter is inserted via flexible bronchoscopy to the target airways (Fig. 49.4). On the vapor catheter, there is a distal occlusion balloon that isolates the lung segment. An electronically controlled pressure vessel generated precise doses of steam that is then delivered to the isolated airways. Airways do show immediate post-procedural blanching, but there are few specific side effects.

The procedure is irreversible (Fig. 49.5), and large-scale or long-term data is not yet available, but results from pilot trials have shown promising results (Fig. 49.6).

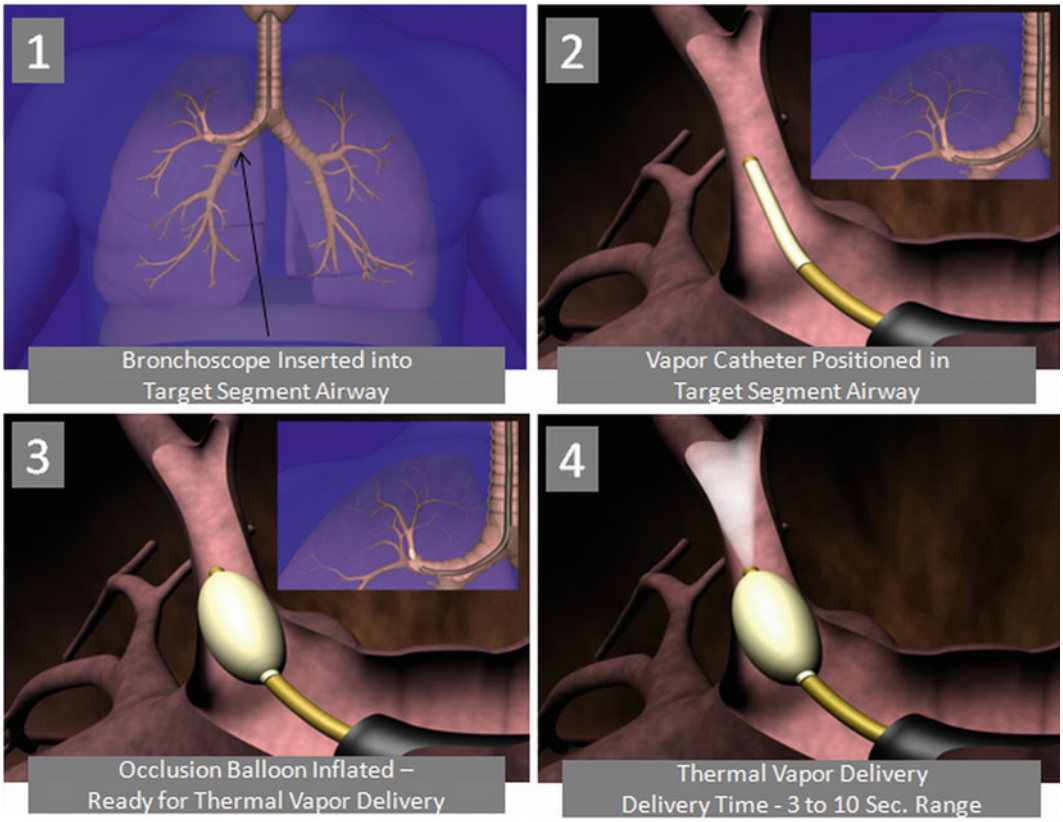

Fig. 49.4 Schematic of treatment stages with steam application (Courtesy of Uptake Medical)

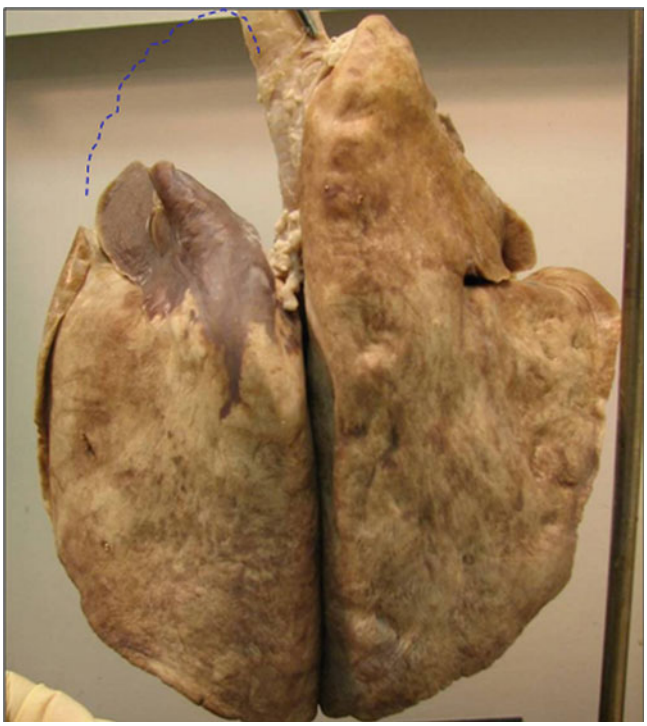

Fig. 49.5 Explanted lung of a sheep treated with steam 3 months prior. The volume reduction in the treated area is clearly visible

Biological Lung Volume Reduction

Biological agents aim to reduce lung volume by blocking off the most emphysematous areas with a rapidly polymerizing sealant. Similar to vapor treatment, the mechanism of action involves resorption atelectasis from airway occlusion, subsequent airspace inflammation, and then remodeling. This remodeling will lead to scarring that induces contraction of lung parenchyma, and functional volume reduction can be expected within 6–8 weeks. The sealant causes blockage of interalveolar as well as bronchiolar-alveolar collateral channels and negates the effects of collateral ventilation.

After identifying a target region, the distal airways in this segment are collapsed by wedging the flexible bronchoscope in the bronchial orifice and applying suction. The liquid sealant in predetermined dose is then injected, and the wedging position is held for a short period of time.

Biological lung volume reduction therapy did bear significant promise. It was instituted in 50 patients with upper lobe predominant emphysema in a phase 2 multicenter trial. Serious adverse events were documented in four patients due to aspiration, pneumonia, pulmonary embolism, and a fall related to analgesia. However, there were no documented

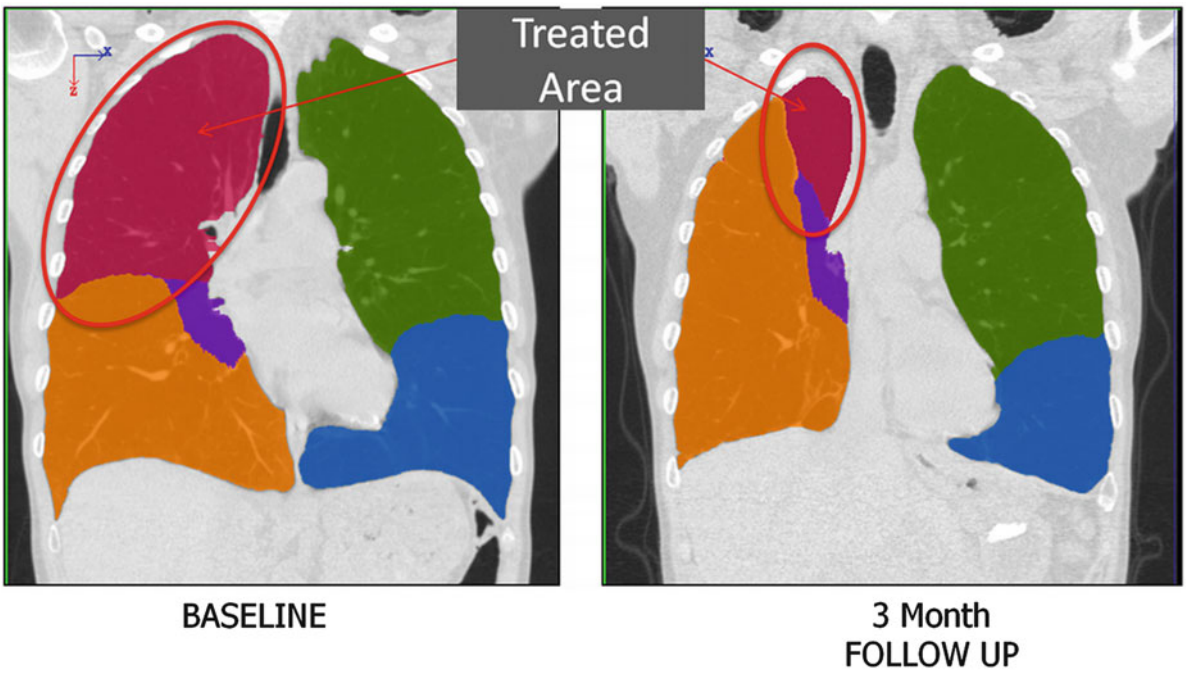

Fig. 49.6 Schematic coloration of an X-ray of a patient who had received steam treatment to the right upper lobe. The *left* image shows the baseline and the *right* image the change after 3 months. The volume reduction of the right upper lobe is delineated

fatalities. COPD exacerbations were observed in 28% (14/50) although three events were thought not to be procedure related. Postoperative leukocytosis, fever, or malaise occurred in 89% over the first 24 h. The primary endpoint of a significant reduction in air trapping was sustained at 6 months in only the patients receiving high-dose therapy (20 ml per subsegment compared to 10 ml). Spirometric improvements and radiological evidence of remodeling were also greater in patients who received high-dose treatment.

Similar efficacy findings and safety profile was found in 25 patients with homogenous emphysema in a subsequent study. Despite having homogeneous emphysema, these patients had poorer perfusion to either the upper lobes or the apical segments of the lower lobes as evidenced by quantitative scintigraphy. Predictably, the most damaged lobes identified by CT also had the poorest perfusion.

Unfortunately, continued studies with the initial preparations were not continued. More recently, similar work has been performed with new injectable formulations, but no phase 2 or 3 data has been reported.

Airway Implants

Airway implants such as nitinol coils of 10–20 cm in length have been designed for use in patients with either homogeneous or heterogeneous emphysema (Fig. 49.7). These implants which are straight when housed in a delivery catheter coil up on deployment and tether the lung. The coils are inserted under fluoroscopic guidance as per CT criteria determined by proprietary protocols (Fig. 49.8). Preliminary safety data have shown no severe adverse events although pneumothorax, pneumonia, COPD exacerbations, transient chest discomfort, and hemoptysis have been reported. Maximal reduction in lung volume occurred between 2 and 4 weeks after implantation (Fig. 49.9), and there is some suggestion of

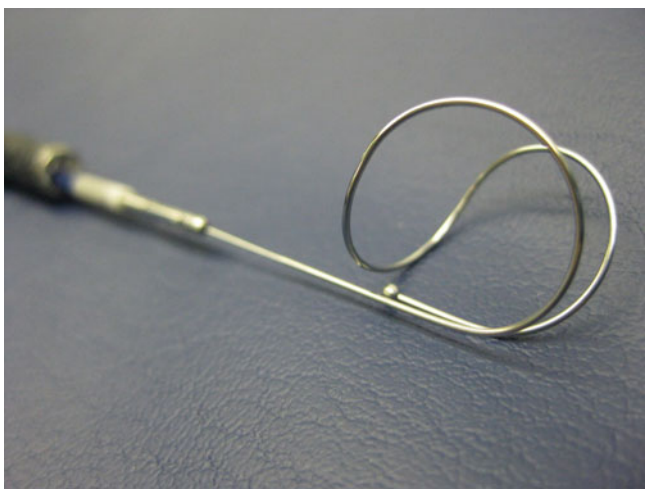

Fig. 49.7 Nitinol implant used for lung volume reduction. Once deployed from the catheter, it assumes a "baseball stitch" configuration (Courtesy of PneumRx)

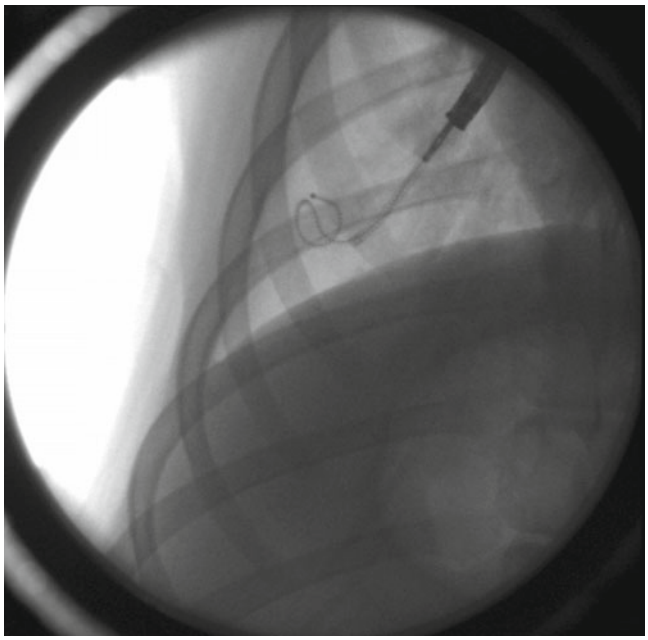

Fig. 49.8 Bronchoscopic placement of a coil implant under fluoroscopic guidance

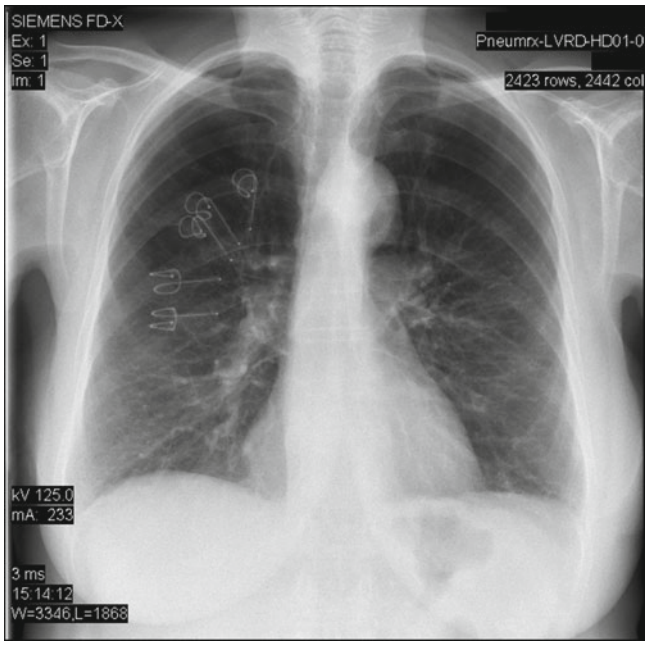

Fig. 49.9 Chest X-ray of a patient who underwent placement of multiple implants for severe upper lobe predominant emphysema

improvements in spirometry, exercise capacity, and quality of life. The trend toward greater improvement was indentified in patients with heterogeneous emphysema and if both lungs were treated. This technique is still in its infancy of development. While encouraging early data has been reported, multicenter and long-term data are still missing.

Airway Bypass Stents

Airway bypass involves the creation of extra-anatomic bronchial fenestrations to deflate emphysematous lung parenchyma. This technique relies on the presence of collateral ventilation which is the ventilation of alveoli through anatomic channels that bypass the airways. These channels include interalveolar pores, accessory bronchiolar-alveolar connections, accessory respiratory bronchioles, and interlobar pathways across fissures. Although collateral ventilation plays an insignificant role in normal lungs, in emphysema where there is increased airway resistance, severely obstructed lung segments are ventilated by these channels. Homogeneity of emphysema is also likely to correlate with the degree of collateral ventilation. In endoscopic airway bypass, newly created low-resistance bronchial fenestrations allow trapped air to escape by bypassing high-resistance obstructed airways. Distal, emphysematous lung segments are drained via collateral ventilation through these fenestrations resulting in a reduction of dead space and air trapping.

Airway bypass procedures are performed on patients with homogenous emphysema. There are three steps that are performed via flexible bronchoscopy: identification of an area of the segmental bronchi that is free from blood vessels using a mini Doppler probe (Fig. 49.10a), fenestration of the airways with a needle balloon catheter (Fig. 49.10b), and placement of a drug-eluting stent (Figs. 49.10c and 49.11). This is to be performed at about eight sites in the lung, which are usually predetermined with the help of CT analysis. Procedures are performed under general anesthesia in intubated patients. The endotracheal tube in combination with a prophylactically placed endobronchial blocking device aims to provide a backup in case the airway fenestration results in massive hemoptysis. This emergency has been reported rarely. Identifying the site with the flexible Doppler probe is not technically difficult, but an identified spot needs to be "remembered," which can introduce unwanted deviation from the target. It is therefore common practice that after penetrating the airway wall with the needle, but before balloon inflation, Doppler examination is repeated. If the site is now positive, it has to be abandoned. Stent placement is performed within the dilated site with the stent mounted on an inflation balloon catheter.

The current data on airway bypass include a multicenter, open-labeled study on 35 patients, as well as a completed randomized, double-blind study involving 208 patients in the intervention arm. Efficacy data at 6 months was found to be limited with no significant changes on spirometry, 6-min walk, and SGRQ. Stent patency at 6 months ranged from 24% to 69%.

Failure to implant stents is a possible intraoperative problem because of either excessive peribronchial blood vessels

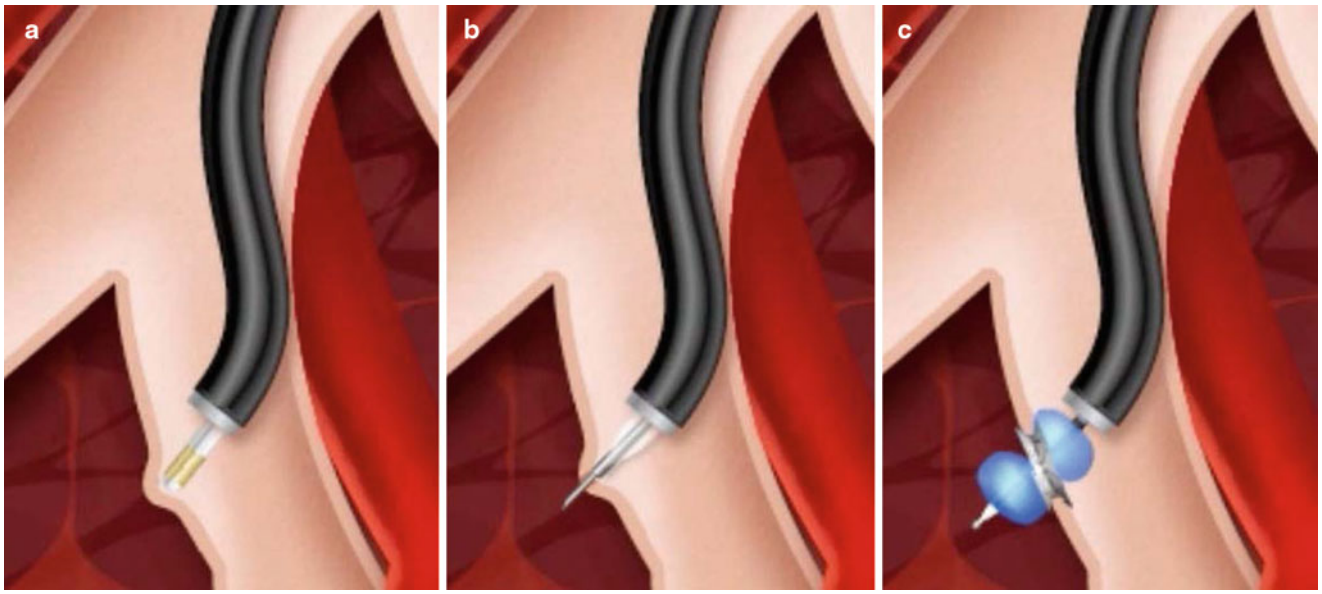

Fig. 49.10 Schematic of an airway bypass procedure from *left* to *right*. A Doppler probe is used to identify areas without adjacent blood flow. Next, fenestration is performed with a needle, followed by placement of a stent to secure the newly created opening

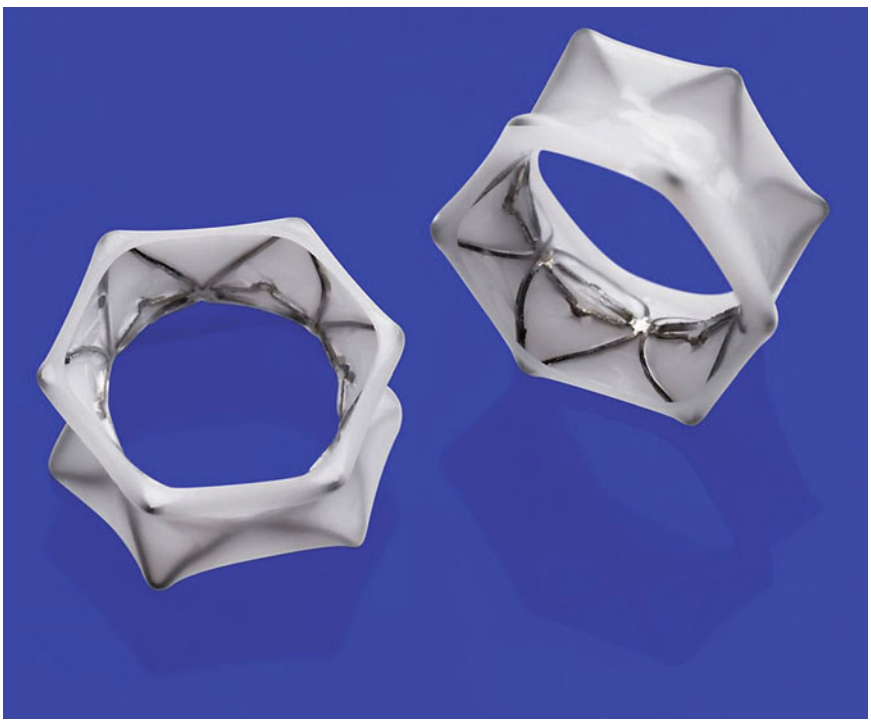

Fig. 49.11 Close up images of a drug-eluting stent placed for airway bypass (Courtesy of Bronchus)

or markedly increased airway wall thickness. Post-procedure complications occurred in 14–59% of cases including COPD exacerbations, pneumomediastinum, and respiratory infections .The current data does not support medium term efficacy of this approach, but it may be that with better device technology, this treatment can be resurrected.

Conclusion

Bronchoscopic lung volume reduction appears to be safer than surgery and presents an attractive alternative to COPD patients who are physiologically fragile. Bronchospasm which is the most commonly reported complication is actually

a recognized complication of bronchoscopy and may not be directly related to any of the volume reduction modalities. However, the efficacy data for all interventions are modest.

In a chronic, debilitating disease such as COPD, improvements in pulmonary function may not be an ideal outcome measure of what is essentially a palliative procedure. Relief of symptoms and enhancement of quality of life may be more realistic goals of future studies. Furthermore, even objective endpoints such as exercise tolerance are heavily influenced by age, cardiac function, muscle conditioning, and comorbidities.

Bronchoscopic lung volume reduction continues to hold much promise. Refining patient selection to identify optimal candidates for each individual endoscopic modality seems crucial and is likely to improve outcomes. Better characterization of emphysema by CT, identifying interlobar fissure integrity, and evaluating collateral ventilation are current directions of research. Perhaps in future, these endoscopic modalities can even be used in combination with endobronchial valves targeting disease in heterogeneously diseased upper lobes, while airway bypass reduces hyperinflation in more homogenously affected lower lobes. Bronchoscopic therapy can also help wean patients off ventilators and may serve as a bridge or alternative to lung transplant.

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Surgical Lung Volume Reduction

50

Walter Weder

Introduction

Emphysema is a progressive and debilitating disease associated with a high rate of morbidity and mortality as a result of respiratory failure. Medical therapy and pulmonary rehabilitation are useful palliative treatment options and can temporarily improve symptoms. However, they do not alter much the natural history of the disease. End-stage emphysema markedly limits the quality of life and survival of patients. Two surgical procedures are well established: lung volume reduction surgery (LVRS) and lung transplantation (LTX). Different endoscopic procedures [1–3] are novel methods showing promising short-term results, but long-term evaluation and randomised trials are necessary to evaluate these methods.

Although the experience with LVRS has grown over the last few years, the selection of patients suitable for LVRS is still a matter of controversy in some patients and differs widely between centres [2–6]. On the basis of the early work from Brantigen [7] and the revival by Cooper [8], the procedure was recommended to be performed as a non-anatomical resection of the most severely destroyed, functionless tissue to reduce lung volume by 20–30%. Bilateral pneumonectomy (volume reduction) was carried out by Cooper using a midline chest incision (sternotomy). We introduced a bilateral video-assisted thoracoscopic approach (VATS) soon thereafter in the early 1990s. Different groups worldwide continued research with LVRS and used both either a unilateral VATS or a bilateral approach. Unilateral resection was performed from a lateral position, whereas bilateral VATS resections were carried out on patients in supine position or with the patient turned around between the two approaches. Some groups preferred a thoracotomy as an incision of choice.

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Several single centre studies and a few small randomised trials demonstrated improved dyspnoea, lung function, exercise capacity and quality of life. Furthermore, these dedicated groups were able to perform LVRS with a perioperative mortality of less than 5%. On the other hand, there were reports on high perioperative mortality as well as no or only short-term benefit from or even harm from LVRS. This led to the initiation of a large randomised trial on emphysema treatment in the USA.

This prospective, multicentre National Emphysema Treatment Trial (NETT) [9] evaluated the outcome of 1,218 patients randomised to either medical treatment or LVRS. The results confirmed that properly selected patients may experience better functional improvements, physical performance and quality of life after surgery than with medical treatment. This was especially the case for patients with upper-lobe predominant destruction of the lungs and a poor exercise capacity. Furthermore, these specific patients in the LVRS group had additionally a lower long-term risk of death than the patients in the medical group. Patients in the so-called high-risk group with an $FEV_1 \leq 20\%$ predicted who had a homogeneous type of emphysema or a $DLCO \leq 20\%$ had an increased risk of mortality (mortality rate was 16% as compared with a rate of 0% to a matched medically treated group) following LVRS and were not considered suitable for LVRS. However, this high perioperative mortality was not a surprise and expected by experienced groups beforehand since these patients were excluded from surgery in their programmes for obvious reasons. A controversy in the indication exists in regard to the morphologic type of emphysema suitable for LVRS.

In most centres, patients who show no heterogeneity in severity of the emphysematous destruction on CT are generally excluded from LVRS because they are judged to experience no or minor benefits only. In these patients, no distinct areas of non- or poorly perfused lung can be identified on perfusion scans as targets for resection, and for this reasons, resection of gas-exchanging tissue seems harmful. However, the favourable effects of LVRS are mainly the improvement

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of respiratory mechanics due to a reduction in static lung volumes, in particular of functional residual capacity (FRC) and residual volume (RV), and this favourable effect may overcome the negative aspects of resection of potentially gas-exchanging tissue. Our group [6, 10] demonstrated that well-selected patients with severe hyperinflation and airflow obstruction benefit from LVRS even if their emphysema was non-heterogeneously distributed. These patients also show a persistent improvement in lung function although to a lesser degree [6, 10].

The concern that patients with non-heterogeneous emphysema who undergo LVRS are potentially at risk of high mortality or worse pulmonary function after surgery is well understandable. Parenchyma, contributing to gas exchange will be resected which has to be compensated by a beneficiary effect of improved respiratory mechanics by downsizing the hyperinflated lung to a more physiologic size. In these patients, the selection criteria should be applied very strictly. Patients only with severe hyperinflation in absence of pulmonary hypertension, with no signs of recurrent infections and especially important, with a diffusing capacity higher than 20% predicted are potential candidates for LVRS.

In a special subgroup of patients, who have emphysema due to an alpha-1 antitrypsin deficiency, LVRS can be considered as a therapy to postpone transplantation [11]. In these patients, with typical involvement of the lower parts of the lung, airway inflammation is often accompanied. However, we observed that only patients without inflammatory signs of the distal airways on CT scan achieved a benefit for more than 6 months and therefore are possible candidates.

Selection of Patients

The selection of patients is based on physiologic concepts, clinical experience and most importantly on emphysema morphology on CT scan. The goal is to select patients with severely symptomatic disease who may benefit from surgery with a low postoperative mortality while excluding those patients at high risk of postoperative mortality and morbidity.

In general, LVRS should be considered for severely impaired patients with dyspnoea, poor physical function, marked airflow obstruction and hyperinflation without medical contraindications known to increase the perioperative complication rate and mortality (Table 50.1). The goal of the NETT study was to assess the safety of LVRS in comparison with medical therapy in patients with emphysema and to identify subgroups of patients that might benefit or have a higher risk from the LVRS. The only prognostic factors associated with differences in mortality between the treatment groups were the craniocaudal distribution of emphysema and the baseline exercise capacity. To distinguish between the low and high exercise capacity, a maximal workload at or below the sex-specific 40th percentile (25 W for women and 40 W for men) was used. In a post hoc analysis, they found that the mortality in patients in the LVRS group with predominantly upper-lobe emphysema and low exercise capacity mortality was lower than in the medical group. A further subgroup analysis revealed that patients with upper-lobe predominant emphysema and high baseline exercise capacity showed no survival benefit from LVRS but an improved exercise capacity, whereas patients with non-upper-lobe emphysema and high exercise capacity had no statistically significant difference in survival nor exercise capacity after LVRS as compared with the medical treatment [12]. Naunheim and colleagues [13] found that patients with advanced age, non-upper-lobe predominant emphysema and steroid use had a higher risk for cardiovascular complications; therefore, it is important to carefully select patients and optimise the preoperative status as far as possible.

Table 50.1 Selection guidelines for LVRS (Zurich)

Inclusion criteria	
COPD with emphysema with severe irreversible obstruction to airflow	FEV1 < 35% pred
Marked hyperinflation of the lung	TLC > 110% pred
Impaired exercise performance	RV > 200% RV/TLC > 0.65 6′ walking < 350 m
Exclusion criteria	
Pulmonary hypertension	PAPm > 35 mmHg
Hypercapnia*	paCO2 > 55 mmHg*
"Destroyed lung" and[a]	DLCO < 20% * and
[a]Homogeneous emphysema	[a]Homogeneous emphysema

However, in our experience, many patients with advanced emphysema consider an improvement in dyspnoea, exercise capacity and quality of life of more importance than the prolonged survival per se. It is obvious that resection of functionless tissue such as in heterogeneous emphysema with or without bullae can be advised to the patient with a relative low risk of mortality and a high chance of significant improvement in dyspnoea, walking distance, quality of life and lung function. FEV_1 improves in a range of 40–80% from baseline with a peak at 3–6 months and lasts for several years.

On the other hand, patients with homogeneous emphysema or patients with alpha-1 antitrypsin deficiency have a less predictable outcome but should not be excluded per se, but selection has to be done particularly cautiously. It is very advisable to exclude all patients from LVRS with an exceedingly low functional reserve such as a diffusing capacity below 20% predicted or with pulmonary hypertension in combination with extreme parenchymal loss (vanished lungs) on CT. However, those patients with homogeneous emphysema who are severely impaired through respiratory mechanics shown clinically by their pathologic breathing pattern, as well as by the depressed diaphragm and distended ribs on chest radiography and

hyperinflation on plethysmography (elevated TLC and RV), are potential candidates when sufficient gas-exchanging tissue (preoperative DLCO > 20%) is left behind. Additionally, cofactors which may potentially interfere with a smooth postoperative course such as previous recurrent infections, known extensive scarring of the lungs or previous surgery have to be taken into consideration in these patients since they are usually not profiting from LVRS over a longer period of time.

Emphysema Morphology

Emphysema is defined anatomically and characterised on CT by the presence of areas of low attenuation. In its severe form, it can easily be detected on a plain posteroanterior and lateral chest radiography. However, the most reliable method of obtaining information on the degree and distribution of emphysema is chest CT scanning. In addition, CT is even more sensitive and more specific than pulmonary function tests for the diagnosis of emphysema. Sanders et al. [14] reported that up to 69% of smokers with emphysema show normal pulmonary function tests.

In our experience, chest CT plays a key role in the selection process for LVRS. Lung densitometry measurements (measuring volumes of zones with different densities) are very helpful for detecting the extent of emphysematous destruction and hence for planning the surgical procedure (Fig. 50.1). In general, areas of fully destroyed tissue are considered for resection, and the resected volume should leave approximately as much lung volume behind as the predicted total lung capacity is calculated. This concept is not validated scientifically by data but seems reasonable to us, and the definition of the lung volume to resect is especially important for patients with homogeneous disease, where target areas are not defined by its destruction. Different morphological grading systems have been developed to quantify the type, severity and distribution of emphysema as a help in identifying candidates for LVRS although no internationally accepted standardised radiological classification exists [15]. A specifically LVRS-oriented classification system based on CT findings was proposed by our group distinguishing between homogeneous, moderately heterogeneous and markedly heterogeneous emphysema distribution, and the predominance of the involved lobes was considered [16].

The following definitions were applied (Fig. 50.2). Markedly heterogeneous emphysema: a distinct regional difference in the severity of emphysema (i.e. decreased density, loss of vascular lung structure) is present in at least two adjacent lung segments of either lung. Intermediately heterogeneous emphysema: a distinct regional difference in severity of emphysema may be present maximally in the area of one or more than one but not in adjacent lung segments of either lung. Markedly heterogeneous: a distinct regional difference in the severity of emphysema is present in at least the area of two adjacent lung segments of either lung. This classification system is easy to apply, helps to select patients for LVRS and allows comparison of outcome. Quantitative perfusion scintigraphy is useful as additive method for confirmation of the target areas for resection.

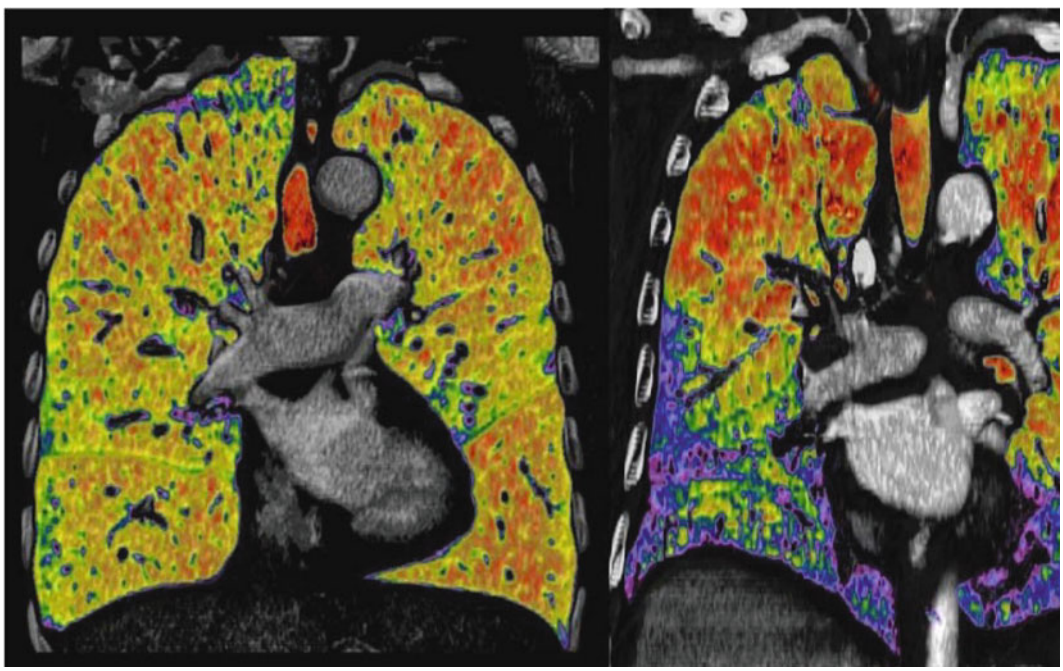

Fig. 50.1 Lung densitometry measurements *left* panel: non-heterogeneous distribution; *right* panel: heterogeneous distribution. Red marks lowest density lair

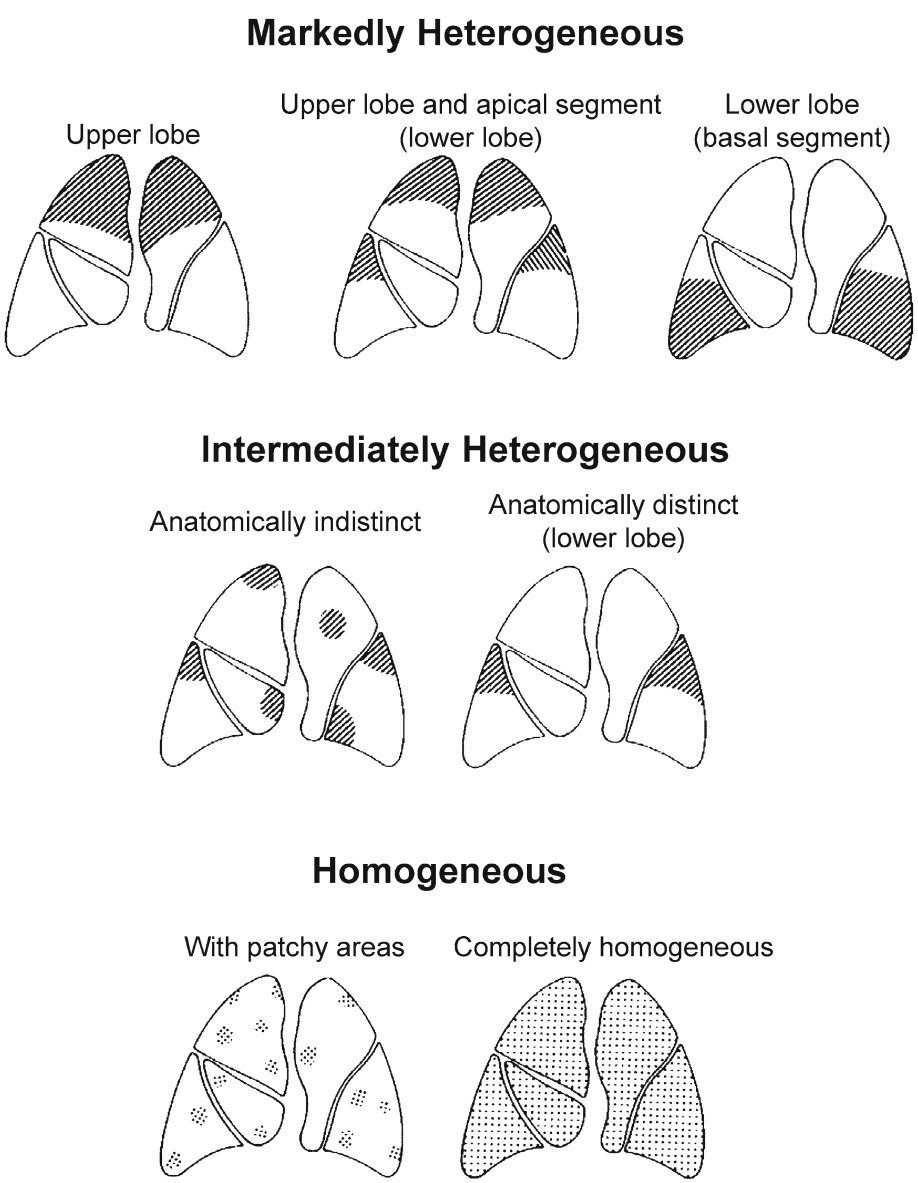

Fig. 50.2 (According to Weder et al. [16]): Classification system of emphysema: Three major types of emphysema distribution were defined: Markedly heterogeneous (*upper panel*), intermediately heterogeneous (*middle panel*) and homogeneous (*lower panel*). For heterogeneous emphysema types, the most affected areas were recorded as disease predominance in either upper lobe, upper lobe and apical segment of the lower lobe, or lower lobe Among homogeneous types of emphysema (*lower panel*), some showed multiple small zones of destruction throughout all lobes (patchy). In other emphysematous changes were evenly distributed throughout the entire lungs (homogeneous)

Lung Volume Reduction Surgery Techniques

LVRS is typically performed under general anaesthesia during one-lung ventilation via either median sternotomy, thoracotomy or VATS (video-assisted thoracoscopic surgery). Staple lines can be buttressed or not buttressed with bovine pericardium or synthetic reinforcement material in order to decrease the amount and duration of air leaks. LVRS is performed uni- or bilaterally. The target areas and the extent of resection differ between various types of emphysema. Staple lines should follow the parenchymal circumference in order to preserve the lung's original shape in relation to the thoracic dimensions and to prevent cavities.

Median Sternotomy Versus VATS

Despite the NETT, the question about the role of median sternotomy or a thoracoscopic approach regarding safety and most efficacious approach for LVRS is still a matter of

discussion, and the approach selected is according to the surgeon's preference.

In 1996, Cooper's group reported their results achieved by a bilateral LVRS through a median sternotomy on 150 patients. The 90-day mortality was 4%. The major complication was prolonged air leak. Kotloff et al.[17] reported on their experience with 120 patients undergoing bilateral LVRS, 80 by median sternotomy and 40 by VATS. The 30-day mortality is not significantly different (4.2% for median sternotomy and 2.5% for VATS); however, the total in-hospital mortality for the median sternotomy group was 13.8%, while it remained 2.5% for the VATS group. There was no significant difference in duration of air leaks or length of hospital stay between the two groups. Functional outcomes achieved with the two techniques were similar. In the NETT [18], 359 patients received lung volume reduction surgery by median sternotomy, and 152 patients by VATS. The 90-day mortality was 5.9% for median sternotomy and 4.6% for VATS. Both techniques had a similar outcome in terms of improved quality of life and functional outcome at 12 and 24 months. The complication rate and morbidities were low for both procedures and did not differ, but the VATS approach allowed earlier recovery at a lower cost than median sternotomy. According to reports and personal communications, most centres in Europe favour the VATS approach.

We prefer a bilateral VATS approach as first choice and observed a 30 day mortality of 0.9% in the last 250 consecutively operated patients.

Unilateral Versus Bilateral LVRS

Several groups compared unilateral with bilateral LVRS. Not surprisingly, they found pulmonary function to be improved more following bilateral than unilateral surgery. However, there are conflicting data in regard to the overall duration of improvement when sequential unilateral surgery was done, but randomised studies were not performed addressing this question. The operative mortality was similar in both groups, whereas long-term survival has been reported to be longer in the bilateral group so that bilateral LVRS became the standard operative technique for patients with severe emphysema [19–21]. However, there is clearly a place for continued selective use of unilateral LVRS typically for patients who are not candidates for bilateral LVRS, in cases with predominantly unilateral disease, tumour or extensive pleural scarring on one side.

VATS Procedure

LVRS by VATS is performed under general anaesthesia with a placed double-lumen endotracheal tube to facilitate sequentially ventilation. A thoracic epidural is advisable to ensure adequate morphine-sparing analgesia so that postoperative pulmonary rehabilitation can proceed immediately after surgery. If the resection is planned on both upper lobes, a supine position is selected which allows an adequate access to both sides of the chest without changing position. On the other hand, the patient is placed in a lateral decubitus position, and changed sequentially when resection is planned on both lower lobes.

For upper-lobe LVRS and the patient is placed in supine, the trocar for the thoracoscope is introduced in the 7th intercostal space in the anterior axillary line whereas the first working incision is usually placed in the 5th intercostal space just lateral to the midclavicular line and the second working incision in the 6th intercostals space in the posterior axillary line. However, the exact position of the working incisions can be modified after visualising the intrathoracic anatomy once the thoracoscope has been placed. For lower-lobe resections and the patient in supine, the incisions are selected one intercostal space distally and more dorsally (midline for the thoracoscope and anterior and posterior axillary line for the lung forceps and staplers).

The lung is resected in areas that show the most severe emphysematous destruction on imaging studies (CT scan) corresponding with loss of perfusion on quantitative perfusion scan (heterogeneous type) [22]. This is typically in the upper lobes (approximately 30–50%) or the basal segments of the lower lobes. Some patients have a combination of upper-lobe (apical) and lower-lobe (apical segment) destruction. In those patients, approximately 20–30% of the upper lobe is resected, in combination with the apical segment of the lower lobe. In patients with homogenous emphysema, it is more difficult to define the amount and site of resection since clearly defined target areas are absent. In these cases, we preferentially choose the upper lobes for resection, and the amount of resection is the volume which is needed to reduce the total lung capacity to its predicted volume, usually approximately 40–50% of both upper lobes as discussed above. Since the resected lung volume cannot be exactly quantified during surgery, the question of the ideal volume of resection cannot be studied scientifically.

Once the resection is completed, the specimen removed and the haemostasis completed, a single 20–24 French chest tube is inserted with the tip oriented towards the apex of the lung, and in case of adhesions with the potential risk of bleeding, a 24-French chest tube is directed towards the diaphragm. The lung is thereafter re-expanded gently using room air with peak airway pressures not exceeding 20 cm H_{20}. The chest tubes are connected to suction (−5 cm H20) or on water seal without suction in order to minimise trauma to the lung due to excessive negative intrapleural pressure (*examples see* Figs. 50.3, 50.4, 50.5, 50.6, 50.7, 50.8, 50.9, and 50.10).

Extubation of the patient in the operating theatre can be regularly achieved with optimal anaesthetic management.

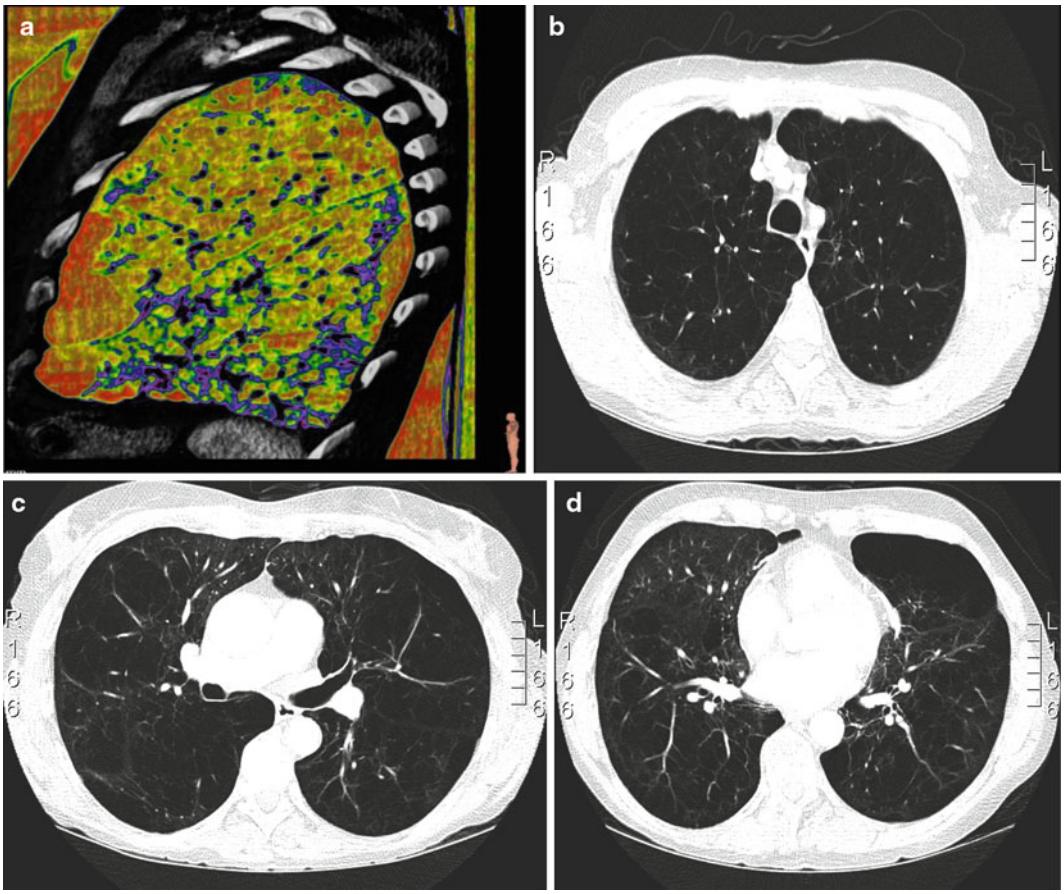

Fig. 50.3 (**a**–**d**) Planning the operative procedure according to the preoperative imaging. (**a**) densitometry of the *left* lung: in red the most destroyed area in the lingula and anterior basal segment of the lower lobe. (**b**) apical segments with intermediate destruction. (**c**) heterogeneous emphysema with better preserved and severely destroyed tissue. (**d**) heterogeneous emphysema with major destruction in the superior lingula segment

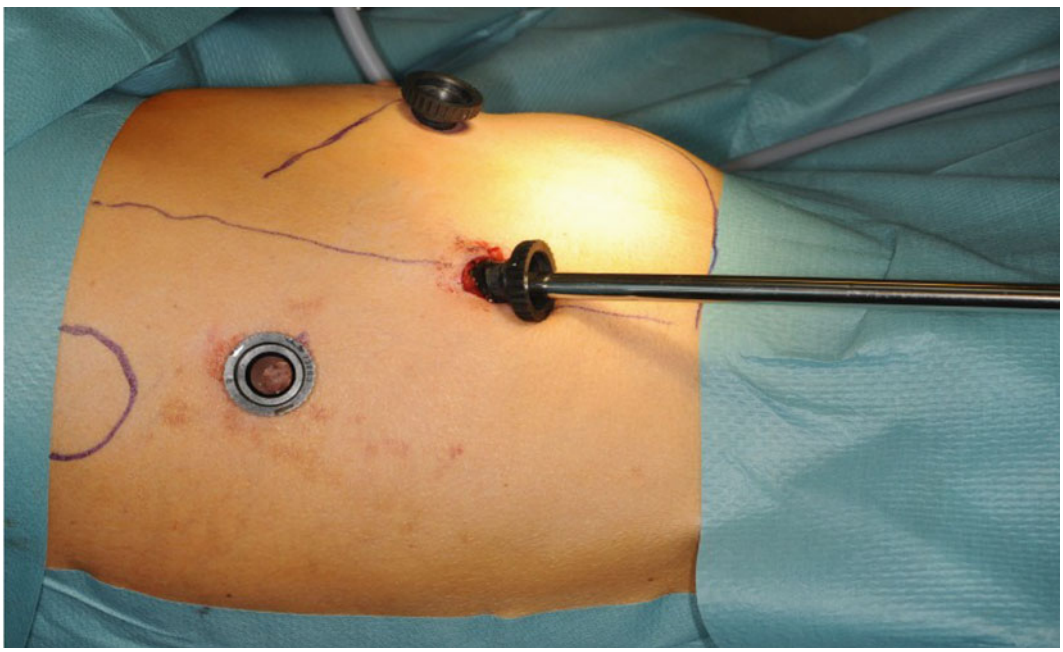

Fig. 50.4 The 10-mm trocars are placed in the 5th and 6th intercostal space, and 30 °thoracoscope is placed through the 7th intercostal space in the mid-axillary line. However, the exact position of the working incision can be made after visualising the intrathoracic anatomy

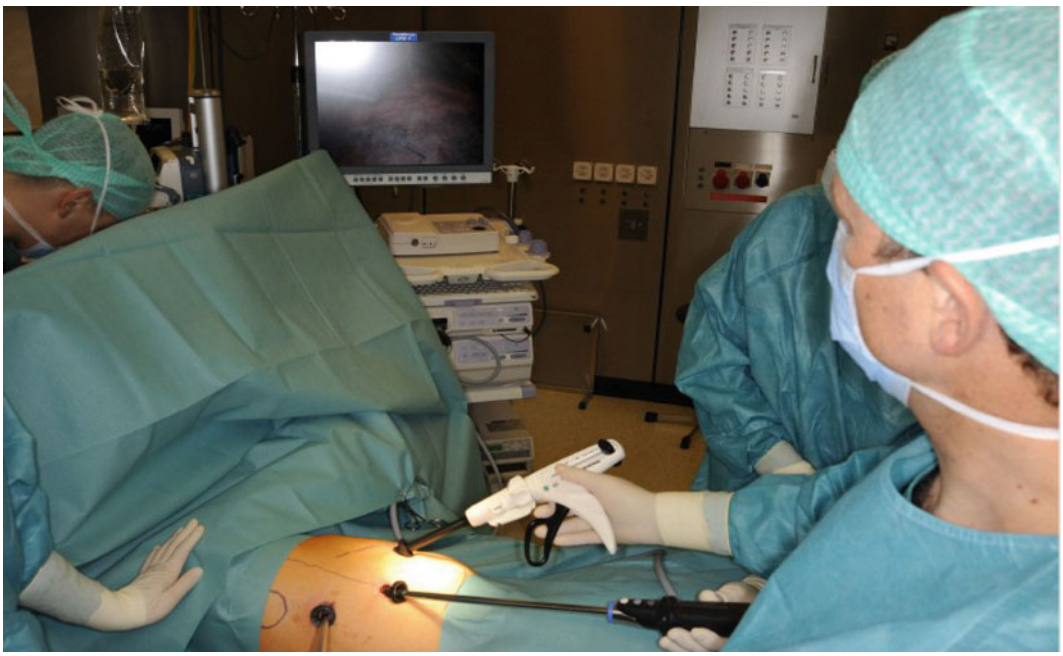

Fig. 50.5 The surgeon can stand on the lateral or opposite side of the patient

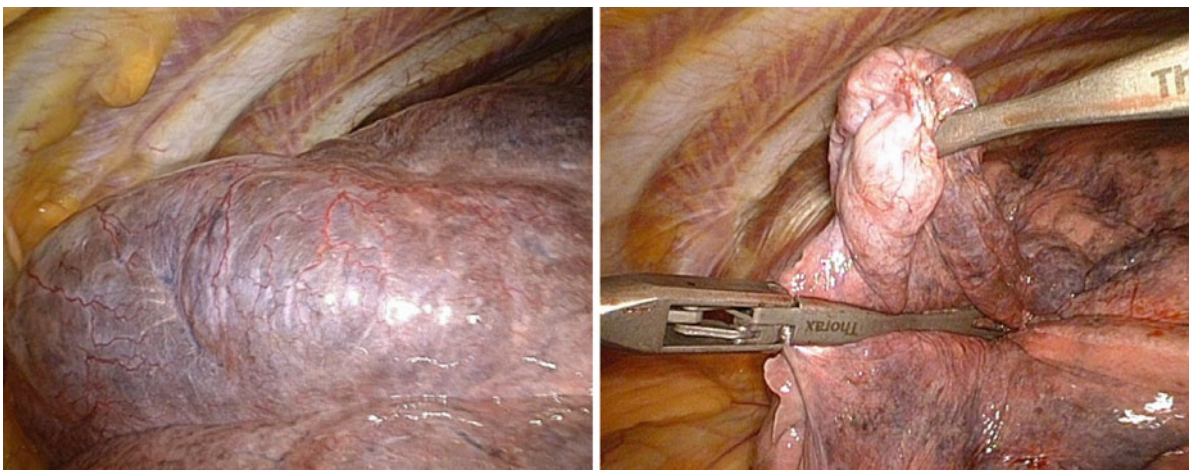

Fig. 50.6 (**a**) Visual inspection of the lungs allows identification of the area for resection. (**b**) careful handling of the lung with thoracoscopic forceps to mimic position of the resection line; with one forceps hold the lung on the edge with the second clamp the lung along the line of the intended resection

Prevention and Management of Air Leaks

The major postoperative complications are air leaks. In the initial reports, approximately 40–50% of patients required thoracic drainage time of more than 7 days. In the recent period, in 266 consecutively operated patients in our centre, the drainage time of more than 7 days decreased to 23%, but 11% still needed a reoperation due to prolonged air leaks. The parenchymal leak is usually not located at the staple line and can be found during reoperation as a pinhole lesion anywhere on the lung surface. Multiple methods to prevent air leaks have been proposed, and various products have been evaluated for this purpose. Buttressing the staple lines is performed with either biological (bovine pericardium) or synthetic material (polytetrafluoroethylene (PTFE)). The duration of drainage time is reduced by 1–2 days in patients who were operated with buttressed staplers. We apply them selectively in

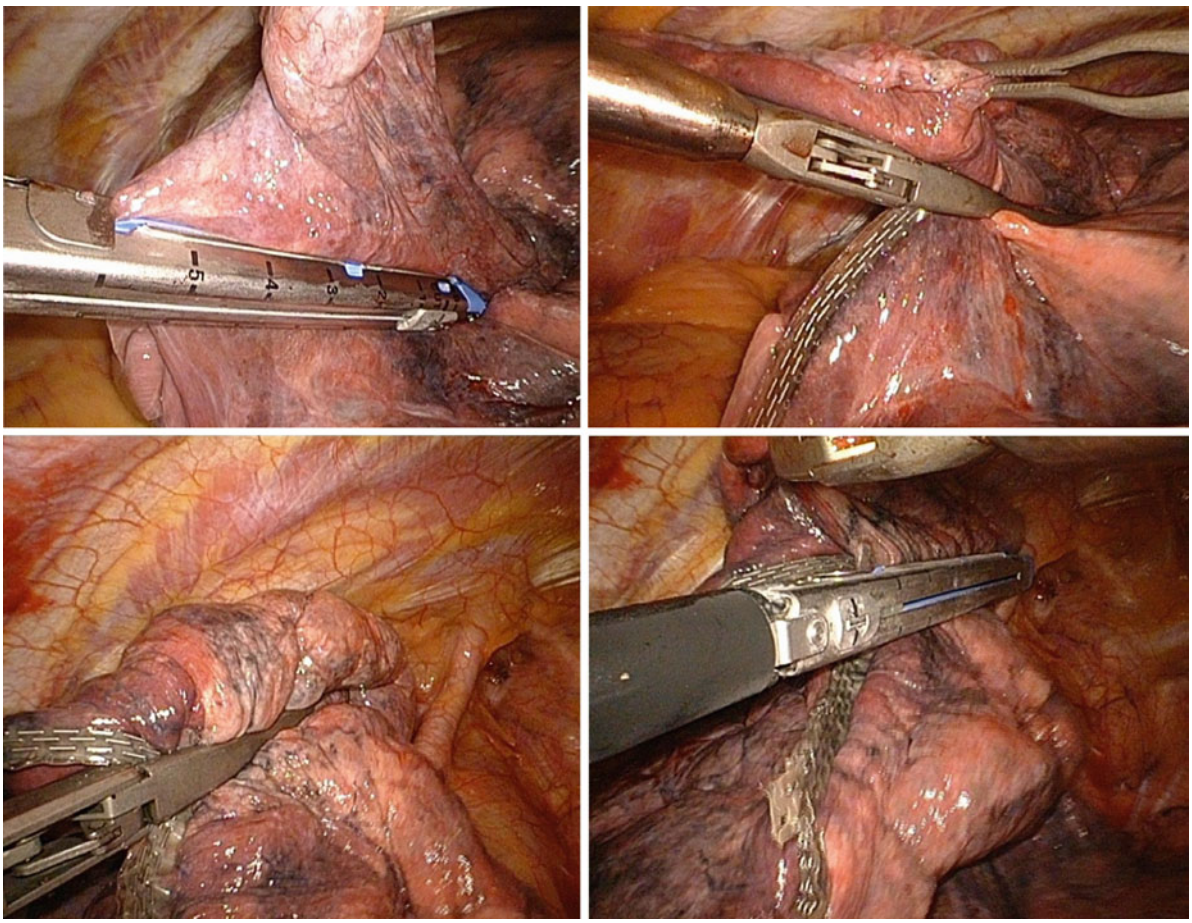

Fig. 50.7 (**a**) Inserting the stapler with buttresses staple lines from distal to cranial. (**b**–**d**) alternating between clamping the lung at the planned resection site and applying the stapler

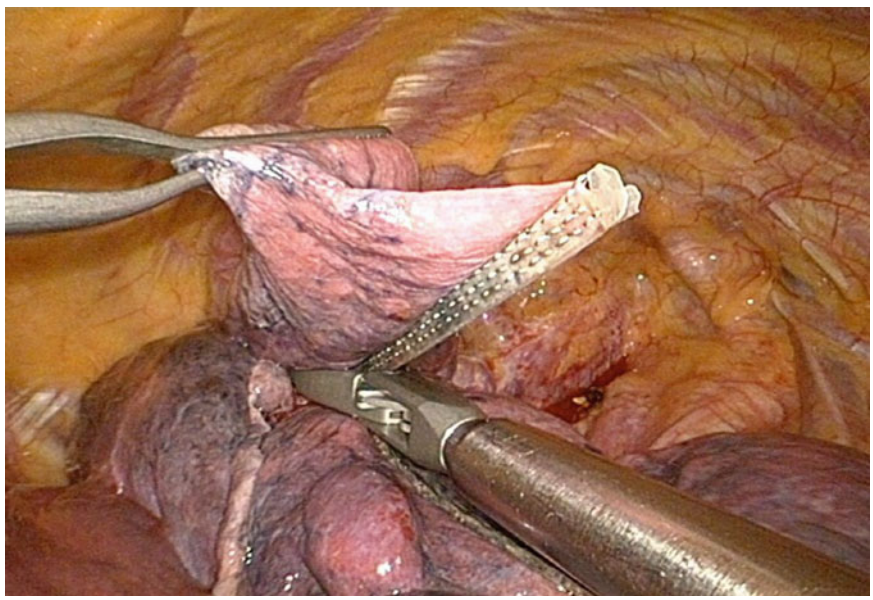

Fig. 50.8 Detail of the resected part with buttresses staple lines

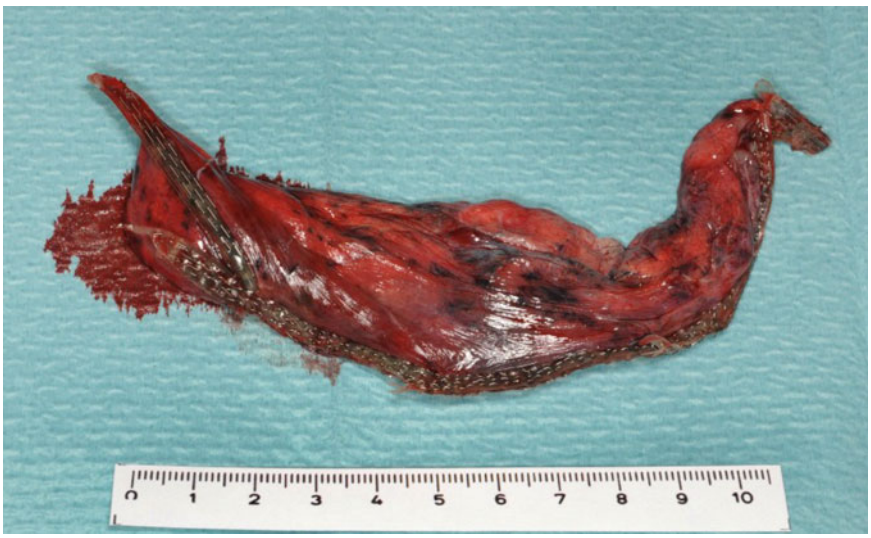

Fig. 50.9 The resected collapsed specimen has usually 30–40% volume of the *upper lobe*

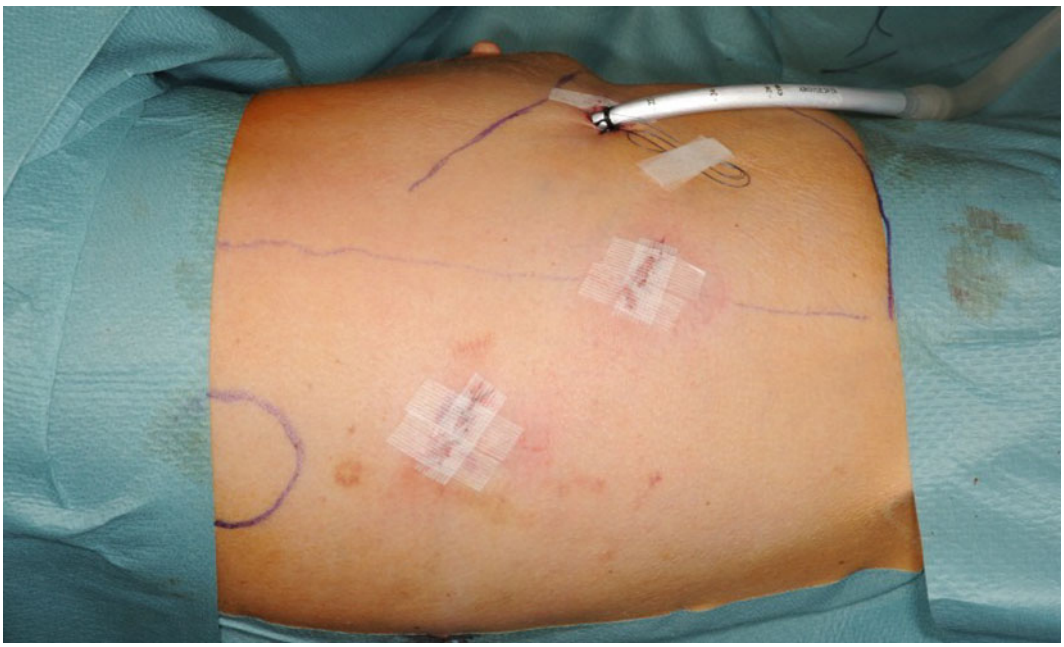

Fig. 50.10 End of operation with steristrips on the incisions

patients with "fragile" tissue at the resection sight but in patients only who are not potential transplant candidates since the adhesions initiated by the buttressing material are usually difficult to dissect later which can be a problem especially at the phrenic nerve.

The NETT study found that an air leak occurred at some point in 90% of patients undergoing bilateral LVRS; the median duration of air leaks was 7 days, and 12% had a persistent air leak even 30 days postoperatively; however, they did not observe any association using buttressed material and the duration of air leaks [23]. Nevertheless, there are randomised studies demonstrating that buttressing the staple line shortens the duration of air leaks and the drainage time [24, 25]. To reduce the incidence of air leaks, several strategies have been developed. Applying low suction (<5 H20 or only water seal alone,) and controlled and cautious reinflation of the lung is very important, as hyperinflation and barotrauma may occur and promote air leaks. Most leaks will seal spontaneously within a few days after surgery, but some even need a reoperation.

Pulmonary Function

LVRS improves significantly lung function and quality of life, with the best results 3–6 months postoperatively. The NETT group confirmed greater functional benefits in selected patients in the surgical cohort when compared with the medical group; this was especially the case in patients with predominantly upper-lobe emphysema and low baseline exercise capacity and in a lesser degree in patients with non-upper-lobe emphysema and low baseline exercise capacity as well.

The improvement may last for up to 5 years postoperatively depending on the morphological emphysema type. Ciccone et al. [4] showed that 6 months after operation FEV_1 increased in 94% of patients with a mean change of 54%. Five years postoperatively, 53% of the patients still had an increase compared to preoperatively. Six months and 1 year after operation, RV decreased by 30%, and 90% of the patients showed improvement. At 5 years postoperatively, 79% of the patients still showed an improvement. The DLCO showed a 25% increase from preoperative values on follow-up at 6 months and 1 year. Gelb et al. [26] found an improvement in $FEV_1 > 200$ ml in 88% of the patients after 6 months, respectively, in 8% after 5 years.

Three months after LVRS, we found relevant symptomatic and functional improvements not only in heterogeneous but in homogenous emphysema type as well (Fig. 50.11). Maximal values were observed 3–6 months after operation with a subsequent decline towards preoperative levels over the following years [27]. FEV_1 increased from 27% to 45% predicted in the heterogeneous group and from 27% to 35% in the non-heterogeneous group and remained significantly improved for up to 3 and 2 years postoperatively, (Fig. 50.11). TLC decreased from 7.77 (±1.5) L to 7.14 (±1.4) L, and RV decreased from 5.31 (±1.3) L to 4.15 (±1.07) L at 3 months after LVRS ($p < 0.001$), resulting in a reduction of the RV/TLC ratio from 0.68 (±0.07) to 0.58 (±0.08) ($p < 0.001$) in the non-heterogeneous group, whereas the RV/TLC ratio decreased from 0.67 (±0.09) to 0.52 (±0.11) ($p < 0.001$) in the heterogeneous group [6]. The beneficial effect on hyperinflation remained statistically significant for up to 2 years in both groups (Fig. 50.11). Independent of the emphysema morphology, the values of FEV_1 and the 6-min walking distance return to values near baseline after a median period of 36 months (Fig. 50.11) although patients perceive persistent improvements in dyspnoea for a much longer time, i.e. for 4–5 years.

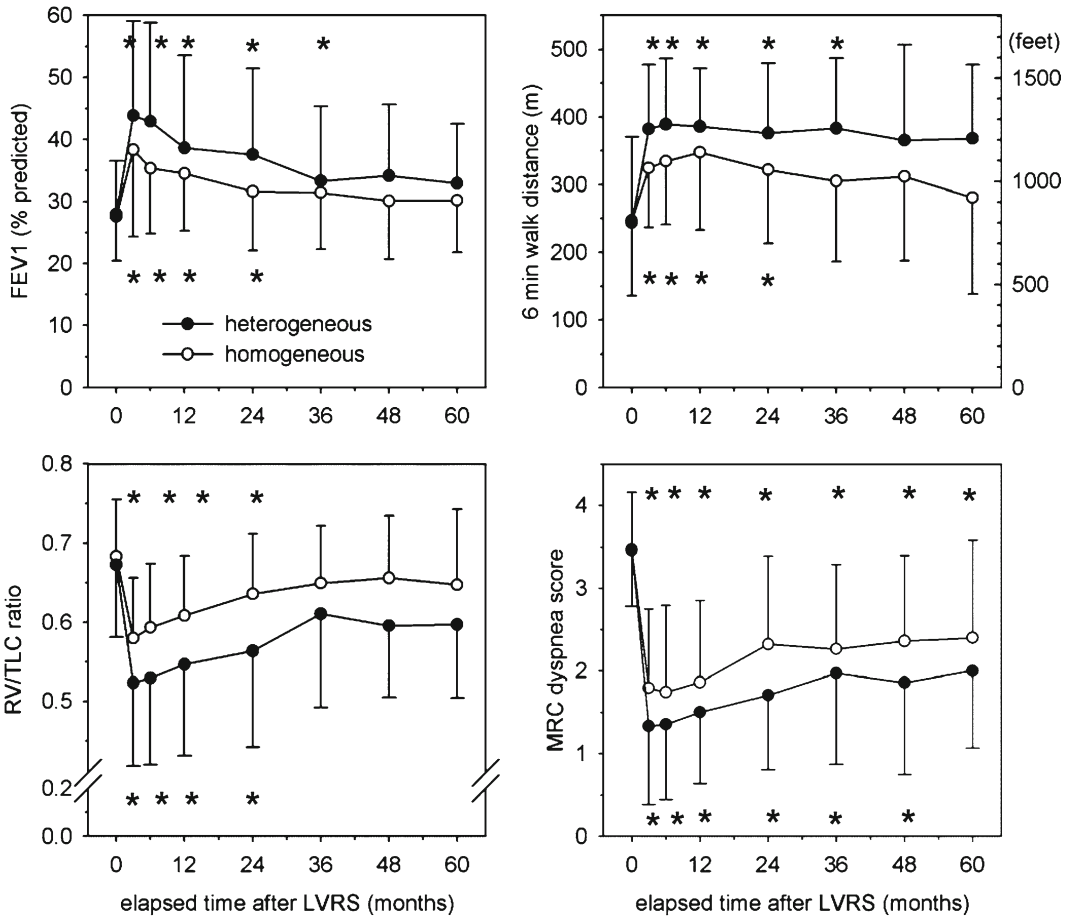

Fig. 50.11 (According to Weder et al. [6]): Time course of FEV_1, RV/TLC, MRC dyspnoea score and 6-min walk distance

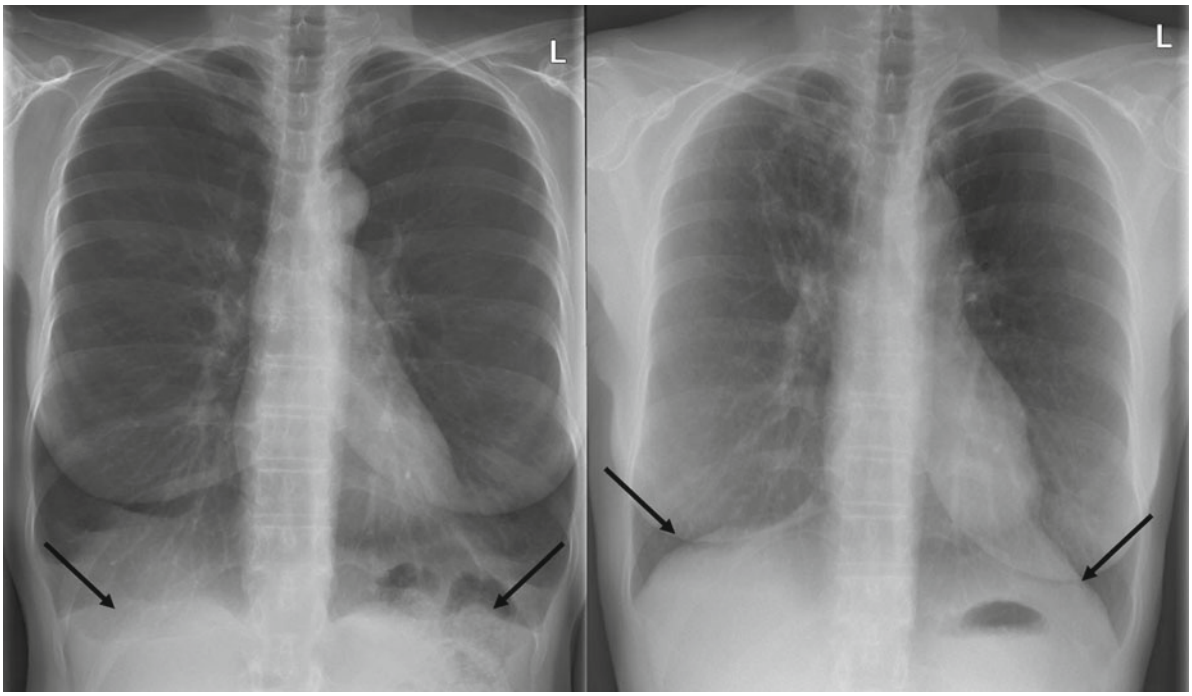

Fig. 50.12 (a, b) Illustrates the effect of LVRS on the x-ray in a patient with emphysema. The preoperative severe hyperinflation of the lung with the depressed and flattened diaphragm is postoperatively clearly diminished, and the chest as well as diaphragm returned to its normal shape

Dyspnoea

LVRS considerably improved dyspnoea in patients with LVRS. Ciccone et al. [4] demonstrated the maximum reduction of the MRC-dyspnoea score at 6 months in 88% of the patients. At 5 years after the operation, 20% of the patients only reported a worse score. Similar improvements were found by Gelb et al. [26] who showed a decrease in the MRC score ≥ in 88% of the patients at 6 months and in 15% after 5 years. In our group, the MRC score decreased significantly in the heterogeneous group by 2.1 points from 3.4 (±0.7) to 1.3 (±0.9) ($p < 0.001$) after LVRS and remained significantly decreased for up to 5 years. In the non-heterogeneous group, it decreased by 1.6 points from 3.4 (±0.7) to 1.8 (±0.9) ($p < 0.001$) after LVRS and remained below baseline for up to 4 years [13].

Survival

The perioperative mortality in centres experienced in choosing and operating emphysema patients is low (2–5%) [4, 5, 20, 28–31]. This was similar in the NETT study after excluding patients from the high-risk subgroup. In the surgical group (1,078 patients were analysed) with either upper-lobe predominant emphysema or non-upper-lobe predominant emphysema and low baseline exercise, the 30-day mortality rate was 2.2% and the 90-day mortality was 5.2%. Naunheim and colleagues [13] demonstrated in their follow-up article an impressive overall survival advantage for the surgical group compared to the medical group, with a 5-year risk ratio (RR) for death of 0.86 ($p = 0.02$). The total mortality rate was 0.11 deaths per person-year in the surgical group and 0.13 in the medical group (overall RR, 0.85; $p = 0.02$).

We observed a 3rd mortality of 0.9% in the last 250 patients operated by bilateral VATS LVRS.

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Endoscopic Asthma Treatment

51

Gerard P. Cox

Introduction

A number of early reports documented severe adverse events associated with bronchoscopy in patients with asthma. However, there is now widespread experience of safely completing bronchoscopy in patients with a range of asthma severity, primarily for research purposes. Using bronchoscopy for therapeutic purposes is less common: either for removal of mucus plugging during acute severe asthma or for performing bronchial thermoplasty in patients whose condition cannot be adequately controlled despite compliance with usual medications.

Bronchoscopy and Lavage for Treatment of Acute Severe Asthma

The use of bronchoscopy in asthma treatment has varied over time. In patients with acute asthma, in whom airways are obstructed by mucus, bronchoscopy may be of value. This is most obvious when there is mucus plugging with segmental, or lobar, collapse. Typically, bronchoscopy allows for removal of a mucus plug and, when effective, is followed by prompt radiographic and clinical improvement. There has been variable implementation of lavage, most often in patients already intubated for mechanical ventilation. In the face of refractory acute severe asthma, bronchoscopy has been performed to enable lavage to remove inspissated mucus from multiple distal airways. This has never been studied in a randomized and controlled trial; rather, published evidence comprises reports of experience with limited numbers of patients. Some authors report treating severe asthma with bronchoscopy for the instillation of mucolytic agents, usually 3–5 ml of a 10% solution of N-acetylcysteine or recombinant human DNase. Despite multiple positive clinical reports from diverse centers, reviews of treatment of acute severe asthma often do not mention this approach.

Bronchial Thermoplasty

In the last decade, bronchoscopy has been used to perform bronchial thermoplasty. This involves delivery of heat treatment to the asthmatic airway in order to redress the accumulation of airway smooth muscle which occurs as part of remodeling events in asthma.

Asthma is a common disease which, in most countries where it has been surveyed, appears to be becoming more prevalent. Patients with mild or moderate disease can enjoy excellent control of their condition should they comply with guidelines for asthma management that have been produced by a number of expert groups. We have learned from large-scale studies that even in the presence of satisfactory symptom control, many patients with asthma remain at risk of suffering exacerbations of their disease. In addition to disrupting their life, exacerbations may require unscheduled office visits, the need for emergency room care, or even hospitalization. Since exacerbations have been found to be associated with marked impairment of quality of life, reducing the rate at which exacerbations occur has become an increasingly relevant outcome for both patients and health care providers.

However, patients with more severe disease often continue to suffer suboptimal control of their asthma despite using standard medications in appropriate regimes. This minority of asthma patients need more effective treatments than are currently available. We are making progress through the development of new anti-inflammatory therapies that target specific pathogenetic mechanisms. Thus, for those patients who have the relevant abnormality, treatment with neutralizing antibodies to immunoglobulin E is widely used, and more recently, studies have shown benefits with antibodies to tumor necrosis factor and interleukin-5. While inflammation is a

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Fig. 51.1 Alair® Bronchial Thermoplasty Catheter (in expanded position) and Alair RF Controller that delivers radiofrequency energy

fundamental abnormality in asthma, many of the symptoms patients experience are due to contraction of airway smooth muscle, causing bronchoconstriction. In addition to having increased sensitivity, the airway smooth muscles contract to a greater degree than in the normal airway. Increased mass of smooth muscle in the bronchial wall is a central element of the remodeling that occurs in chronic asthma. To date, there is no medical therapy that effectively reduces the increased mass of muscle found in the airways of patients with asthma.

Bronchial thermoplasty is performed at bronchoscopy and involves the delivery of radiofrequency (RF) energy to the airways that is converted to heat in bronchial tissue. The design of the treatment catheter and the parameters (duration, amount) for RF energy delivery were optimized during preclinical studies of tissue responses in both ex vivo and in vivo animal airways. At its distal end, the catheter has an expandable array of four electrodes (Fig. 51.1, Alair® Bronchial Thermoplasty Catheter and Alair RF Controller). The level of RF energy used for bronchial thermoplasty is much lower than that used for cautery or tissue ablation. Since the target temperature in the airway is only 65 °C, the tissue is heated but not burned and there is usually no visible effect of thermoplasty treatment. At present, complete treatment of the human bronchial tree requires three bronchoscopies that are usually done 3 weeks apart. Each procedure includes approximately 20–30 min of treatment time and may take up to 45–60 min when preparation time is considered. Either the nasal or the oral route can be used. Some operators prefer using an oropharyngeal airway or endotracheal intubation, but this is not essential. Adequate topical anesthesia is very important and typically involves solutions and gels of lidocaine of varying concentrations, that is, 1–4%. There are local variations in achieving local anesthesia; some use nebulized solutions, some use pledgets soaked with lidocaine that are directly applied, and some use sprays. As with all procedures, an accurate accounting of drug dosing is important – but is especially important with bronchial thermoplasty as the procedure is prolonged compared with usual bronchoscopy, and thus it is feasible to exceed the maximum safe dose of lidocaine of 7 mg/kg. One member of the procedure team should have specific responsibility for tracking drug usage. Unless using general anesthesia, adequate sedation is most often achieved using intravenous medications, usually a benzodiazepine and a narcotic. Some centers are appropriately equipped and staffed to use propofol, but most operators use medications such as midazolam 5–10 mg and fentanyl 50–100 μg or their equivalent. While local standards might vary, it is essential that appropriate monitoring of heart rate and rhythm, blood pressure, oxygen saturations, and level of sedation are in place along with full capacity for resuscitation. I am not aware of any patient requiring intubation and ventilatory support after thermoplasty, but as the procedure is performed increasingly widely, it is a foreseeable event.

It is important at the first bronchoscopy to survey and map the subject's bronchial tree to enable planning of the treatment sessions (Fig. 51.2, Airway Worksheet). Any variations in anatomy and any irregularities of the bronchial tree, such as cartilaginous spurs or pigmentation or unusual vascularity, should be noted. The airways are treated systematically – starting as distal as possible under direct vision and working proximally, ensuring a continuous treatment effect to the airway wall (Fig. 51.3: BT treatment). As mentioned already, there is usually no immediate visible effect of treatment. Occasionally, a pale streak (blanching) may be seen when the electrode array is withdrawn (Fig. 51.4: blanching at BT treatment site). The array can become contaminated with mucus and epithelial debris after a number of activations. When this happens, it should be removed from the bronchoscope and cleaned with gauze soaked in sterile saline. Bleeding can occur but most often is trivial and self-limited. Preoperative management is aimed at optimizing the patient's asthma and preventing immediate deteriorations. Thus, patients receive prednis(ol)one 50 mg or equivalent for 3 days prior, the morning of the procedure, and the day following the procedure. Pretreatment spirometry should show that the FEV_1 is above 80% of maximum values and bronchodilator – albuterol or equivalent by nebulizer or inhaler – is

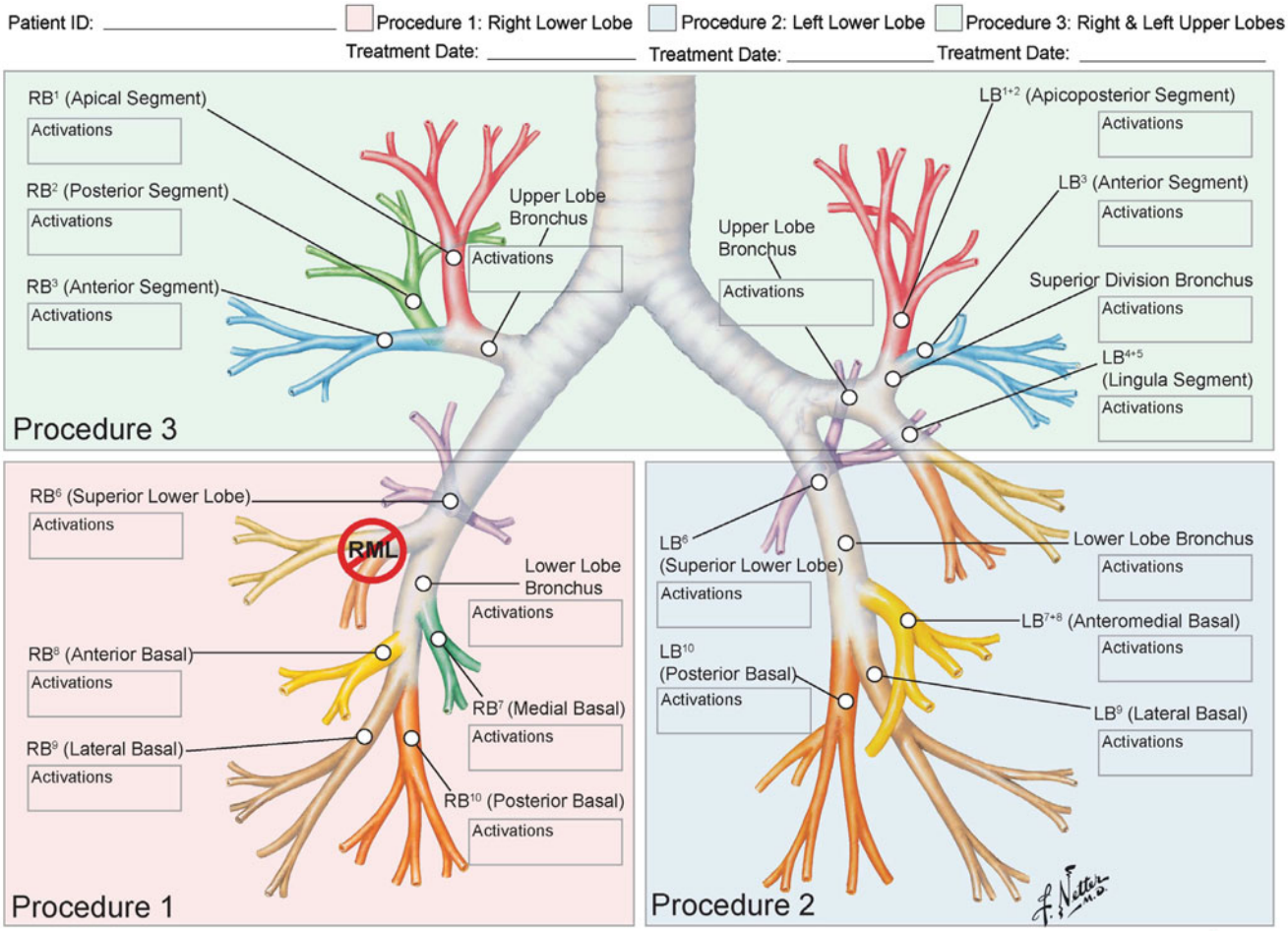

Fig. 51.2 Airway Worksheet for (**a**) mapping of accessible airways that will be treated, note right middle lobe is not treated, and (**b**) logging of all complete and incomplete activations of treatment catheter

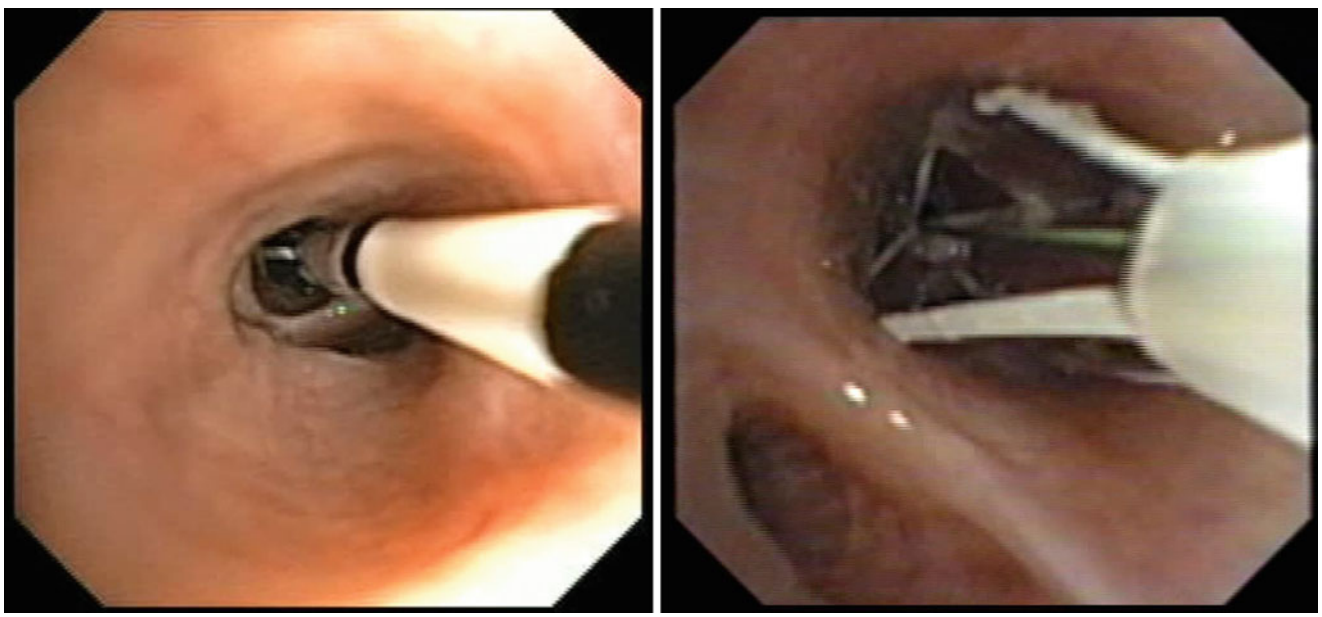

Fig. 51.3 (**a**) and (**b**) BT treatment images: Electrodes have been collapsed and catheter will be withdrawn to next treatment site. Note *black marker* bands on the distal catheter that are 5 mm apart to facilitate precise placement of the electrodes Catheter expanded in situ for activation. Note epithelial and or mucous accumulation on the uppermost electrode. Occasionally, when excessive, this requires removal of the treatment catheter for cleaning

given routinely before the procedure. Bronchospasm has been noted during treatment and can be reversed with local instillation of a dilute solution of bronchodilator if it interferes with completing the procedure. Postoperative symptoms of bronchitis – dyspnea, cough, sputum, wheeze, and chest tightness – are common and should be treated with inhaled bronchodilators such as albuterol and ipratropium along with protocol-directed 2 days of prednis(ol)one 50 mg/d. Documented infections are uncommon, but clinicians have typically had a low threshold for prescribing antibiotics to patients after bronchial thermoplasty, probably motivated by the knowledge that the bronchial epithelial layer has been breached.

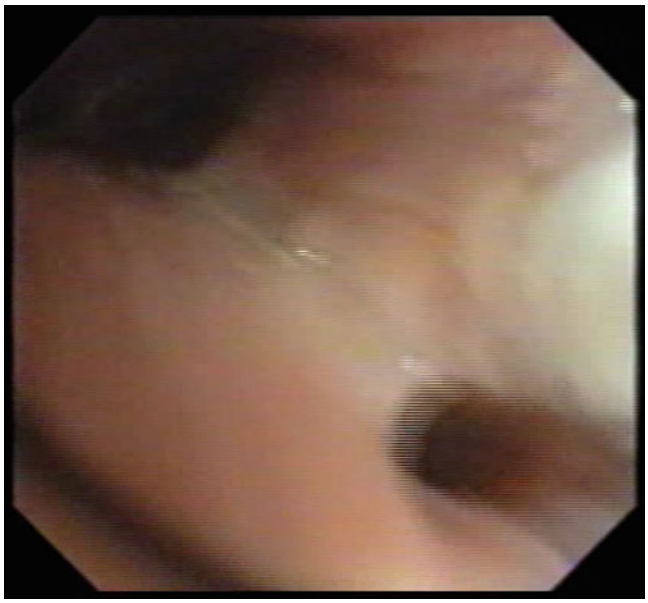

Fig. 51.4 Airway wall immediate posttreatment showing pale streak (blanching) where contacted by the electrode

The first application of bronchial thermoplasty in a patient with asthma was in 2000. Since then, three randomized controlled clinical trials have been completed comprising 260 subjects, with moderate or severe asthma. The published experience documents the safety and efficacy of bronchial thermoplasty with follow-up out to 5 years. In 2010, both the FDA and Health Canada approved the use of bronchial thermoplasty for the treatment of severe asthma.

The initial report showed it was feasible to carry out bronchial thermoplasty in patients with mild or moderate asthma. Subsequently, three randomized, controlled trials have examined the safety and efficacy of bronchial thermoplasty in moderate and severe asthma: Asthma Intervention Research (AIR), Research in Severe Asthma (RISA), and the AIR2 trials. Table 51.1 provides demographic data on the subjects enrolled in these trials. The severity of asthma, as indicated by medication needs and airflow obstruction, increased across the feasibility, AIR, and RISA studies. The selection criteria for AIR2 were modified to exclude subjects with highest risk of requiring hospital admission for management of worsened asthma symptoms after treatment. Among the predictive factors for such worsening were higher requirements for oral corticosteroids and lower levels of FEV_1. There was evidence of benefit following bronchial thermoplasty in all four studies, and the various outcomes are given in Table 51.2.

Table 51.1 Demographic data on subjects treated with bronchial thermoplasty

	Feasibility	AIR	RISA	AIR2
# Treated with BT	16	55	15	190
Female (%)	10 (63%)	31 (56%)	9 (60%)	109 (57%)
Mean age (yrs)	39 ± 8.6	39 ± 11.2	39 ± 13	40 ± 11.9
ICS (μg BDP equiv.)	900 ± 424	1,351 ± 963	2,333 ± 817	1,961
Criterion	N/A	≥200	≥1,500	≥1,000
LABA (μg salmeterol)	100 (5)*	111 ± 36	125 ± 60	117 ± 34
Criterion	0–100	≥100	≥100	≥100
OCS (prednisone)	0	0	14.4 ±6.2 (8)*	6.4 ± 2 (7)*
Criterion			≤ 30 mg	≤ 10 mg
Pre-BD FEV_1 (%pred)	82.3 ± 13.4	72.6 ± 10.4	62.9 ± 12.2	77.8 ± 15.6
Criterion	60–85%	60–85%	≥ 50%	≥ 60%
Symptoms criterion		Worsening after LABA withdrawal	≥8/14 days	≥ 2/28 days

Four trials have examined effect of bronchial thermoplasty in subjects with asthma of varying severity. The inclusion criterion for the demographic variable is given where applicable and comparison of these for ICS, OCS, and FEV_1 provides an indication of asthma severity among the four trials. Data are given for mean and standard deviation. *When not all subjects in a group were on the specified therapy, the number who were is given in parentheses and the mean refers to that subgroup

BT bronchial thermoplasty, *ICS* inhaled corticosteroid, *LABA* long-acting beta-agonist, *OCS* oral corticosteroid, *BD* bronchodilator

Table 51.2 Outcomes indicating benefit of treatment with bronchial thermoplasty

Feasibility	AIR	RISA	AIR2
PEF	AQLQ	AQLQ	AQLQ*
BHR	Rescue meds	Rescue meds	Time lost (work/school)
Symptom-free days	Symptom-free days	Asthma control questionnaire	E-R visits
	Exacerbations* (mild)	(OCS use) ($p=0.12$)	Exacerbations (severe)
	PEF		

A range of outcomes indicating asthma control have been examined in the four trials. Both the feasibility and RISA trials examined safety as their primary outcome. The primary outcome for the AIR trial was exacerbation rate, and was AQLQ for the AIR2 trial, indicated by (*)
PEF peak expired flow, *BHT* bronchial hyperresponsiveness, *AQLQ* asthma quality of life questionnaire, *OCS* oral corticosteroid, *E-R* emergency room

Not surprisingly, most subjects experience an increase in symptoms related to airway irritation after bronchial thermoplasty. Typically these increased symptoms are temporary, presenting soon after treatment and resolving in less than 7 days. As studies have enrolled subjects with increasing severity of asthma, the frequency and severity of adverse events occurring after the bronchoscopic procedures have increased also. Those with more severe asthma are at risk of requiring hospitalization for management of exacerbations of their asthma, because of their relative insensitivity to usual medications (particularly corticosteroids) and more severe baseline condition. Once the treatment period is complete, that is, at 6 weeks from the last treatment bronchoscopy, the rates of adverse events in the treated groups are equal to those in control subjects, indicating the temporary nature of treatment-related symptoms. Thus, the experience to date is that treatment-related adverse events are temporary and predictable but potentially serious especially in patients with more severe asthma (defined by lower FEV_1 and chronic use of higher doses of systemic corticosteroids).

In all three randomized trials that have been completed, treated subjects showed improvement in various objective measures of asthma severity or control. Thus, bronchial thermoplasty has the potential to benefit patients with mild, moderate, or severe persistent asthma. Patients who have the most severe asthma, defined by complex treatment regimens, prior hospitalizations, excessive rescue medication use, and reduced lung function, are at higher risk for complications of bronchoscopy. But these are the patients for whom new treatment approaches are most needed. Regarding less severe asthma, it is likely that those whose symptoms can be well controlled with regular use of modest doses of conventional medications would not be inclined or encouraged to undergo bronchial thermoplasty. Expert commentators have frequently observed that bronchial thermoplasty might be of greatest benefit to patients with brittle asthma, who suffer profound airflow obstruction that develops rapidly, often with little or no notice or warning. Thankfully, this condition is uncommon but it is obviously extremely unnerving for all, including patients, their families, and health care providers. Thus, while an optimal selection process has yet to be developed for considering who best to recommend for bronchial thermoplasty, the procedure is likely to be most appropriately offered to those with more substantial disease burden from asthma, with higher medication needs, less predictable disease course, and more frequent or severe exacerbations. Among the subjects participating in the trials to date, there are a number of recurring themes in their discussions of why they found a procedure such as bronchial thermoplasty attractive. Many are seeking a treatment that has longer-term benefit – they find the continuous reliance on a number of medications coupled with the uncertainty of what might happen very intrusive and restrictive. In addition, any intervention that has the potential to reduce the frequency or severity of exacerbations is of great interest to patients with asthma.

Longer-Term Outcomes

During the early evaluation of bronchial thermoplasty, there was considerable discussion around the potential for development of long-term adverse consequences. Thermoplasty is expected to cause structural changes in the airways which are known to undergo remodeling events as part of the asthmatic condition. Whether there could be an interaction with chronic inflammatory events added another uncertainty. Data from long-term follow-up of the subjects who participated in the randomized trials are becoming available. Upon study completion, subjects were invited to take part in observational studies out to 5 years which comprised clinical, radiological, and airflow assessments. The data on 5-year follow-up of patients participating in the AIR trial show no evidence of late-developing adverse consequences of bronchial thermoplasty. One subject who had exited from the AIR trial underwent resection of a lung abscess. Detailed examination of the airways to the affected site did not reveal any evidence of abnormality following bronchial thermoplasty. Rates of severe deterioration in asthma control requiring hospital attendance have been found, not surprisingly, to vary over 5 years but show no evidence of deterioration over

time. Spirometry results show stability of airflow over 5 years, in both pre- and post-bronchodilator values for FEV_1 and FVC. Chest X-ray examinations do not show any new changes developing over time. Thus, concerns about the potential to develop bronchiectasis with chronic infection, airway stenosis, and atelectasis have not been realized. Thus, long-term follow-up studies show no late increase in adverse events; rather the benefits in asthma control following bronchial thermoplasty have been found to persist.

Current Status of Bronchial Thermoplasty

Since FDA approval was given in April 2010, a number of centers in the USA have initiated programs providing bronchial thermoplasty to patients with severe asthma who continue to suffer regular symptoms despite using current standard-of-care medications, including but not limited to ICS and LABA. While the published methods provide a template for how to perform the procedure, certain local influences result in differences. Thus, in a minority of settings, the procedure is performed under general anesthetic instead of under moderate conscious sedation. Also, there is variation in sedation protocols which reflects local expertise. Thus, some centers use propofol rather than the more widely used combination of midazolam and fentanyl.

Building on the substantial experience gained during the completion of the research trials, a number of centers in South American and European countries now provide bronchial thermoplasty. The list of active centers is expected to grow rapidly in the next few years as will our collective experience. At present, the role of bronchial thermoplasty for managing asthma is under discussion by those who assemble guidelines, but no major organization has defined its position yet.

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Image-Guided Ablation Treatment for Lung Cancer Patients

52

Damian E. Dupuy

Introduction

Primary lung cancer is the second most common cancer and leading cause of death in both men and women in the United States. An estimated 222,520 new cases of lung cancer are expected in 2010, accounting for about 15% of cancer diagnoses, and an estimated 157,300 deaths, accounting for about 29% of all cancer deaths that are expected to occur in 2010. Lobectomy and complete lymph node dissection remains the standard procedure and offers patients the best chance of long-term disease-free survival. However, only about one-third of patients are surgical candidates. Sublobar resections are a compromise surgery in high-risk patients and may lead to higher local recurrence rates unless the primary tumors are smaller than 2 cm. Medically inoperable patients due to advanced age and cardiovascular comorbidities have traditionally been treated with radiotherapy. Older 3D conformal radiotherapy techniques with 5-year survival rates as low as 15% are being replaced with newer stereotactic techniques that show excellent local control rates as high as 92%. Radiation toxicity can still be problematic in the highest risk patient, and more precise tumor treatment can be accomplished with percutaneous image-guided techniques such as radiofrequency ablation (RFA). Since these percutaneous image-guided techniques are minimally invasive, they allow reduced morbidity and mortality, conserving the normal lung tissue, and lower procedural cost. Thermal ablation is suitable for real-time imaging guidance and possible to perform in the outpatient setting. RFA and other thermal techniques such as microwave or cryoablation are minimally invasive treatments that are commonly used with this sicker group of patients. This chapter will discuss these modalities, show clinical examples of their implementation, and review the pertinent literature.

Currently, image-guided thermal ablation procedures are best suited for medically inoperable, high-risk patients with early stage lung cancers. Those patients could qualify for surgical resection but are medically inoperable largely due to severe cardiopulmonary disease. Patients with small, oligonodular, and favorably located pulmonary metastatic lesions without hilar or mediastinal nodal and extrathoracic involvement and patients who seek palliative measures for tumor-related symptoms or chest recurrences within treatment fields are also suited for this procedure. Recent medical literature reports that approximately 50% of patients were dying without adequate pain relief. The three main causes of malignancy-related pain are osseous metastatic disease (34%), Pancoast tumor (31%), and chest wall disease (21%). Common complications during the course of the disease include pain, dyspnea, cough, hemoptysis, metastases to the musculoskeletal system and central nervous system, obstruction of the superior vena cava, and tracheoesophageal fistula. Therefore, palliative care is a crucial part of treatment, however often times not successfully achieved. The newer alternatives such as percutaneous image-guided thermal ablation procedures may be a viable salvage modality, which will at minimum provide symptomatic relief. In addition, thermocoagulation causes cytoreduction, which allows external beam therapy and chemotherapy to be more effective. Thermal ablation may be a safe procedure even in patients with limited pulmonary reserve and technically feasible for unresectable pulmonary malignancies. The goal of thermoablative therapy is to prolong disease-free survival with a reasonable quality of life. Patients who are stable enough to undergo computed tomography-guided needle biopsy are good candidates for lung tumor ablation. Patients with severe pulmonary fibrosis and

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severe emphysema with limited life expectancy (less than 1 year) should be considered poor candidates as they will likely die of their comorbidities and not of their early stage lung cancer.

Patients are initially evaluated clinically (history, physical examination, blood analysis, etc.) and explained of the risk (such as bleeding and serious cardiopulmonary issue such as severe restrictive or obstructive lung disease or poor cardiac function) and benefits of the procedure. Side effects of the procedure may include post-ablation syndrome – a systemic response to the circulating factors such as tumor necrosis factor that results in fever, malaise, and anorexia. Other complications including mild-to-moderate intraprocedural pain (usually controlled with adequate analgesics), mild pyrexia (usually self-limiting and lasting up to several weeks), pneumothorax, hemorrhage, hemoptysis, bronchopleural fistula, acute respiratory distress syndrome, reactive pleural effusion (usually self-limiting), damage to adjacent anatomic structures, skin burns (secondary to inappropriate grounding pad placement for RFA), and infection or abscess formation can occur but have been reported in less than 1% of cases.

The energy in the radiofrequency and microwave spectrum (10^9–10^{11} Hz) can possibly interfere with cardiac devices. Therefore, coordination with the patient's cardiac electrophysiologists and careful positioning of the grounding pads should be made. External pacing/defibrillation should be available for emergency use.

Most procedures are performed under midazolam and fentanyl sedation, although in certain situations, when procedural pain is problematic and in pediatric patients, a general anesthetic or monitored anesthesia care (MAC) with propofol may be required. VanSonnenberg et al. report using intercostal and paravertebral nerve blocks with long-acting local anesthetic to prevent postprocedural discomfort and pain. There are also reports of cryoanalgesia effect in the intercostal nerves during CA procedures. During the procedure, patients undergo monitoring with continuous pulse oximetry and electrocardiography and measurement of blood pressure every 5 min.

To reduce potential complications of the sedation, patients are treated after an overnight fast. On the day of the procedure, patients with hypertension and cardiac issues are recommended to take their medications as usual. Insulin-dependent diabetic patients are asked to administer only half of their usual morning insulin dose. A short physical examination is performed, and an intravenous lane is placed right before the procedure.

The skin entry is determined using a computer grid according to preprocedure CT images (Fig. 52.1). The area is then prepared in a sterile fashion, and local and deeper extrapleural lidocaine anesthesia is administered.

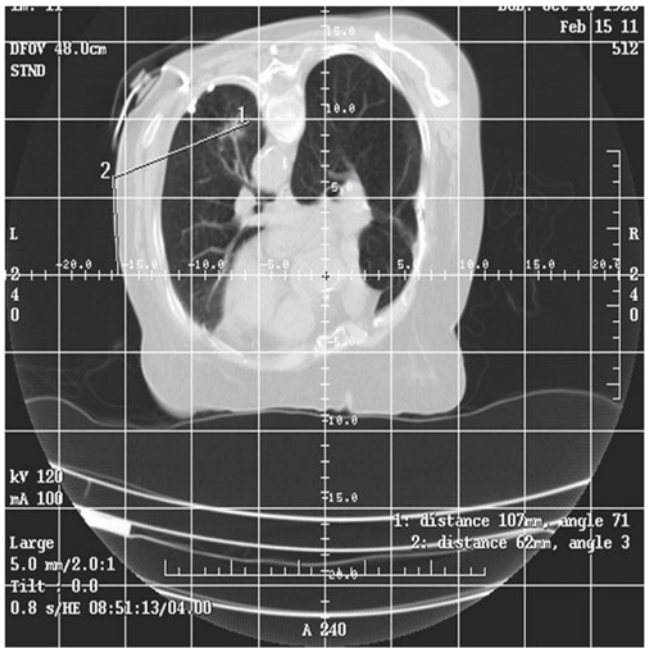

Fig. 52.1 An 84-year-old woman with left lower lobe adenocarcinoma was referred for microwave ablation. (**a**). Axial CT image with the patient prone shows the computerized grid that is used to select the safest skin entry site, trajectory, and distance to the tumor. On the lower right of the image, the distance in mm (*line* 2) from the lateral laser light indicates the skin entry site for that particular CT slice (e.g., table position), and *line* 1 indicates the distance in mm and trajectory angle perpendicular to the tumor

Radiofrequency Ablation

In RFA, an electrode connected to an RFA generator is placed directly into the target tissue. A reference electrode (grounding pad) is placed directly on the patient's skin, in an area with good electrical conductivity (usually thigh or opposite chest wall). When an electric current in the frequency of radio waves (460–480 kHz) is applied, tissue heating results from resistive energy loss (frictional heating) as electrons collide with molecules in tissue as they move back and forth in the electrical circuit The goal is to heat tissue to 60–100 °C. This temperature is considered lethal to target tissue. Energy generated during the radiofrequency (RF) ablation procedure is accumulated within the lung mass because the normal lung parenchyma acts as an insulator and therefore concentrates the RF energy in the target tissue. There is also a "heat sink" effect, from medium to large blood vessels and airways which dissipates heat away from the normal adjacent tissue and concentrates the energy within the solid component of the target lesion. This same effect may limit successful RF ablation of larger lesions.

CT fluoroscopy is used to assess placement of the needle and to plan trajectory of the RF electrode (Fig. 52.2a).

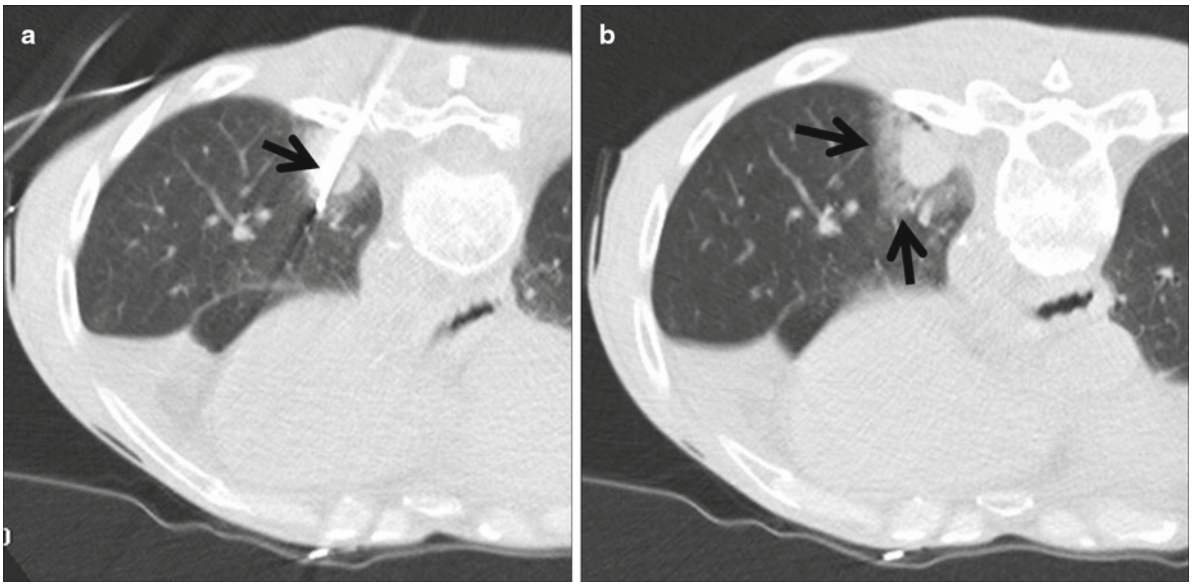

Fig. 52.2 A 60-year-old man with left lower lobe adenocarcinoma felt to be a poor candidate for lobectomy due to underlying lung disease and previous radiotherapy. (**a**) Axial CT fluoroscopic image shows a cluster RF electrode within the mass. (**b**) Axial CT fluoroscopic image with the needle removed shows the typical ground-glass halo that surrounds the tumor (*arrows*).The halo gives a rough indication of energy penetration into the aerated lung around the mass

The choice of electrode length and the active tip length are chosen according to the size and depth of the lesion. Some RF electrodes have an internal thermocouple that measures temperature in the tissue. Some are also coupled to an infusion pump to internally cool the electrode tip (to prevent tissue charring which reduces current deposition) or to directly infuse saline into tissue to improve thermal and electrical conductivity. RFA treatment times vary between 2 and 20 min in one position depending upon the dielectrical properties of the tumor, adjacent tissue, and local thermal sinks such as larger vessels and bronchi. Electrode used in RFA may be a single tip, a cluster electrode (3 closely spaced electrodes), or multiple deployable tines which can obtain thermocoagulation diameters from 2 to 5 cm.

Once the target lesion is treated, the RF electrodes are removed and CT-guided fluoroscopy is performed to evaluate for a pneumothorax and treat it if needed. All patients are observed 4–6 h in the recovery room, and a repeat chest radiograph is obtained to confirm the absence of a pneumothorax.

Microwave Ablation

Microwave ablation (MWA) like RFA uses heat to coagulate tissue. Electromagnetic microwaves traveling at 9.2×10^8 Hz produce friction and heat by agitating water molecules within the surrounding tissues and causing the molecules to flip. This procedure induces coagulation necrosis and cell death. To maximize the interaction of the water molecules, microwave radiation can specifically be tuned to the natural frequency of water molecules. Temperature is used to measure the amount of heat generated depending on how fast the water molecules oscillate within the target lesion.

Microwave ablation has been successfully utilized in treatment of hepatic malignancies by several groups. Larger tumors (greater than 3 cm) may require the use of multiple MWA applicators to create a large enough area of thermocoagulation. There are currently two MW frequencies (915 and 2,450 mHz) that are available for clinical use. The lower frequency can penetrate deeper into tissue and requires less power. The higher frequency is absorbed more and therefore requires more power. Antenna shaft cooling may not be necessary at 915 mHz but is definitely required at 2,450mHz due to the conduction along the shaft that may lead to thermal damage along the needle tract. Single or multiple MW antennas may be needed to achieve the desired volume of tissue necrosis. Grounding is not necessary with microwave ablation. Unlike RFA, tissue charring is not a significant limitation of electromagnetic wave propagation used in microwave ablation.

Cryoablation (Cryotherapy) Technique

Percutaneous cryoablation (CA) allows gas in a region of constant temperature to travel down the shaft of the cryoprobe through an aperture into an area of lower pressure thereby allowing the gas to expand and become cooler (Joule-Thompson Effect). Argon gas allows expansion from high

pressure to low pressure through a constricted orifice (J-T port) within the cryoprobe at ultracold temperatures (approximately −160 °C) and forms an "ice ball" as a marker for identifying the ablative margins. At the end of the procedure, helium gas is used to warm the probe and facilitate removal. Each CA treatment at a given cryoprobe position consists of a 10-min freeze, followed by an 8-min thaw, and subsequently followed by another one 10-min freeze. Faster ablation schemes using a 3-min freeze, 3-min thaw followed by 7-min freeze and thaw, and a final 5-min freeze have been proposed to improve the zone of ablation and slightly shortening the ablation time to 25 min compared to 28 min.

The cryoablation procedure is based on the freeze-thaw-freeze technique, with osmotic shifts causing cellular membrane rupture and eventual cell death. The resulting endothelial damage leads to platelet aggregation and microvascular thrombosis.

Follow-Up

Imaging studies immediately after the procedure and during follow-up are necessary to measure the success or failure of the initial procedure, interval growth and need for repeat ablation, and metachronous tumor development. Unfortunately, at the current time, there is no proven imaging modality or time interval for immediate post-ablation and subsequent imaging to accurately depict success or failure of the initial ablation.

During and immediately after RFA ablation, CT can be used to identify and analyze the tissue changes that occur in the lung around the ablated mass which has been referred to as a ground-glass halo (Fig. 52.2b). This imaging appearance is a very rough approximation of margin of tissue necrosis, and the exact zone of tissue death is somewhere in the middle of this finding. There may be wrinkling of the edges, vaporization, and "cockade phenomenon" which demonstrates concentric rings of varying density. The tumor diameter may decrease or may not change during treatment depending upon tumor type. At 1-month follow-up, the lesion may appear as an area of consolidation and nodularity, and the diameter will be larger than before ablation (Fig. 52.3). There may also be cavitations and "bubbly lucencies." Successfully treated lung tumor also shows decreased contrast enhancement. PET is also useful in the follow-up evaluation. A decrease or complete absence of FDG activity (photopenia) is suggestive of necrosis with no residual tumor (Fig. 52.3). If there is residual or recurrent tumor, there is increased FDG uptake within the periphery of the lesion. False-positive PET within 6 months can be seen with a pleural reaction (Fig. 52.3). Akeboshi et al. demonstrated that PET was more sensitive than contrast-enhanced CT to detect early tumor progression.

On initial post-ablation contrast-enhanced CT scans, MW ablated tumors demonstrated the effects of thermally induced necrosis. A hazy ground-glass opacification was most common. At 1-, 3-, and 6-month intervals, ablation zones increased in size due to thermal changes in adjacent lung tissue, followed by a persistent reduction in diameter consistent with consolidation. There were also cavitary changes identified (Fig. 52.4). Ablated tumors abutting the visceral pleura resulted in pleural thickening in 34% of ablation zones in 44% of patients or pleural retraction in 5% of ablation zones in 8% of patients.

Kawamura et al. report about follow-up CT chest scans of patients who underwent cryoablation (Fig. 52.5) that were carried out at 1-month and then 3-month intervals. Changes in tumor mass after cryoablation were measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) protocol, which is based on objective measurements of lesion size before and after treatment. The response to cryoablation according to RECIST was at the rate of 50%. The response rate of each tumor was 54.3%.

Presently, thermal ablation is best used for patients with early stage lung cancer who are not surgical candidates, patients with small and favorably located pulmonary metastases, and patients in whom palliative care of tumor-related symptoms is the goal. Without this treatment, the majority of patients with lung cancer (86%) die of their disease. The overall 5-year survival rate for all clinical stages is dismal at 14%.

The literature regarding the outcomes of thermal ablation is diverse, since study groups are heterogeneous and follow-up periods, reporting, and evaluation are different. Outcome reporting is difficult.

Simon et al. retrospectively reviewed 153 consecutive patients with 189 primary or metastatic inoperable lung cancers who received RFA and a median 20.5-month follow-up period. The long-term Kaplan-Meier median 1-, 2-, 3-, 4-, and 5-year survival rates for stage 1 non-small cell lung cancer were 78%, 57%, 36%, 27%, and 27%, respectively, demonstrating a survival benefit especially in nonsurgical candidates. The corresponding survival rates for colorectal pulmonary metastases were 87%, 78%, 57%, 57%, and 57%. However, most of these patients received prior and/or adjuvant chemotherapy; therefore, the sole effect of RFA is difficult to evaluate. The local tumor progression-free rates at 1, 2, 3, 4,and 5 years were 83%, 64%, 57%, 47%, and 47%, respectively. Tumor size was a statistically significant predictor of local tumor progression.

De Baère et al. followed 60 patients with 5 or fewer tumors per patient, with a diameter of less than 4 cm. Ninety-seven of 100 targeted tumors were treated and showed an overall survival rate at 71% and a lung-disease-free survival at 18 months of 34%. At 18 months, the overall survival rates were 76% for primary lung tumors and 71% for metastatic disease. This study also reports a 54% rate of pneumothorax, with chest tube placement in 9% of the procedures.

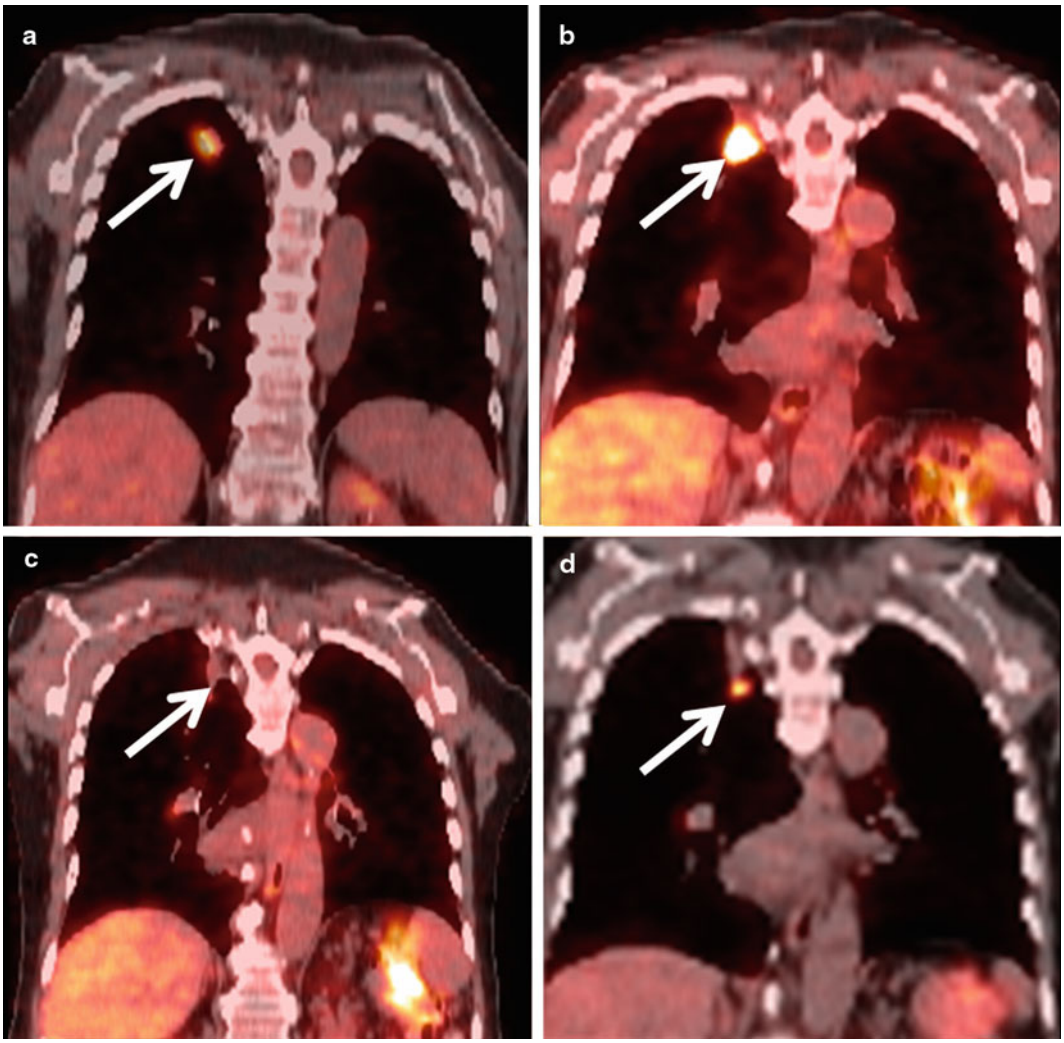

Fig. 52.3 An 84-year-old man with right upper lobe squamous cell carcinoma. (**a**) Coronal PET/CT shows the FDG-avid cancer in the right upper lobe (*arrow*). (**b**) Six months after RFA coronal PET/CT shows extensive FDG-avid pleural-based soft tissue (*arrow*) which was biopsied and shown to be inflammatory tissue. (**c**) Repeat PET/CT 1 year after RFA shows interval resolution of FDG activity with the thermal scar (*arrow*). (**d**) Eighteen-month follow-up PET/CT shows a new nodule below the ablation scar that is FDG avid (*arrow*) which was subsequently shown to be recurrent cancer on biopsy

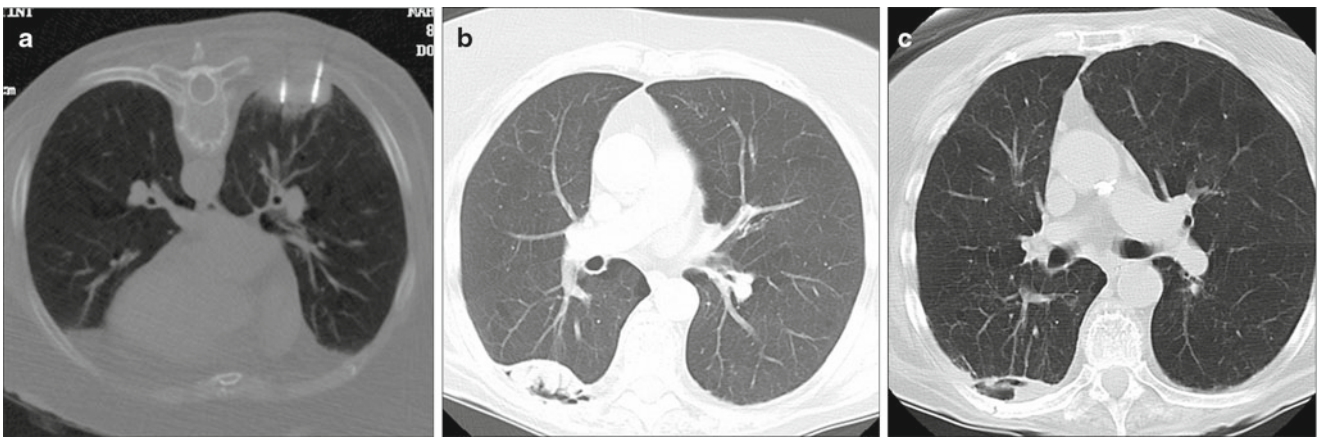

Fig. 52.4 An 85-year-old woman with 5-cm right lower lobe non-small cell lung cancer was referred for microwave ablation due to poor performance status and dementia. (**a**) Prone axial CT fluoroscopy image shows two of the four microwave antennae used to treat this cancer. (**b**) Axial CT image 1 year after the ablation shows internal cavitation of the mass (*arrow*). (**c**) Axial CT 52 months after the ablation shows interval shrinkage of the thermal scar and persistent cavitation (*arrow*)

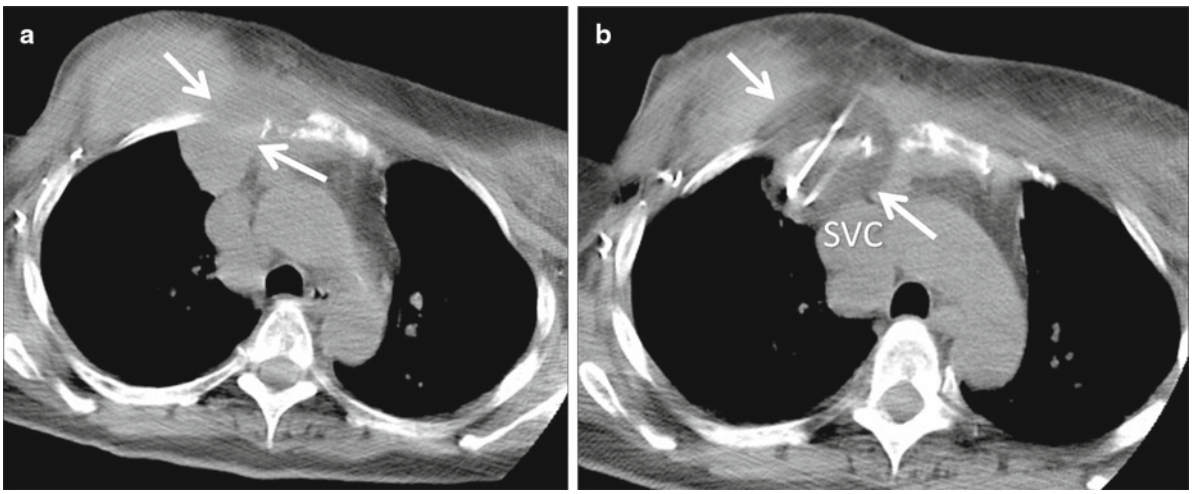

Fig. 52.5 A 60-year-old woman with recurrent breast cancer invading the right anterior chest wall despite chemotherapy and radiation. The patient was referred for palliative cryoablation due to unremitting pain. (**a**) Axial CT image shows the mass (*arrows*) extending through the chest wall and abutting the mediastinum. (**b**) CT image during the freeze cycle shows the low density ice ball (*arrows*) extending up to the superior vena cava in the expected location of the right phrenic nerve. The patient's pain improved 2 days later, and she was able to reduce her narcotic requirement

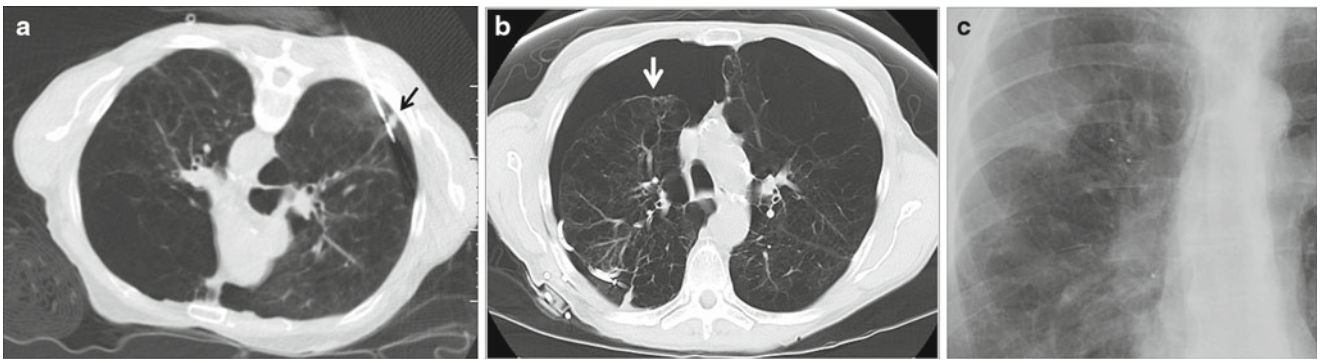

Fig. 52.6 A 65-year-old man with severe oxygen-dependent emphysema and a small right lower lobe non-small cell lung cancer. (**a**). Prone CT fluoroscopy image shows a microwave applicator next to the small lung cancer (*arrow*). (**b**). Despite two chest tubes to treat his pneumothorax and 2 weeks of wall suction, a repeat CT shows persistent pneumothorax (*arrow*). (**c**). Interventional pulmonology placed three endobronchial IBV valves to stop the air leak as seen on this PA chest X-ray 1 week after placement

In a study with 50 patients that were treated with MWA, Kaplan-Meier analysis yielded an actuarial survival of 65% at 1 year, 55% at 2 years, and 45% at 3 years from ablation. Cancer-specific mortality yielded a 1-year survival of 83%, a 2-year survival of 73%, and a 3-year survival of 61%; these values were not significantly affected by index size of larger than 3 cm or 3 cm or smaller or presence of residual disease.

Kawamura et al. performed CA on metastatic pulmonary lesions on 35 tumors in 20 patients. The 1-year survival rate was 89.4% with local recurrence of seven tumors in seven patients (20%). Wang et al. studied the feasibility and safety of the procedure for thoracic malignancy and demonstrated that tumor size and location were highly predictive of tumor ice coverage even when controlled for tumor stage and type. A short-term follow-up showed palliative benefits of cryoablation in terms of general health status with increased dietary intake and weight gain.

The greatest advantage of RFA is experience. Most of the studies performed in the field of pulmonary thermal ablation are made with RFA. The main disadvantages of RFA are that the RFA systems are to be avoided in the mediastinum and high in the lung apex, as they can cause mechanical and thermal injury to nerves and larger blood vessels. Pneumothoraces are common but usually managed conservatively or with outpatient thoracostomy drainage with a Heimlich valve. Rarely, persistent bronchopleural fistulas may need intervention with fibrin glue or endobronchial valve placement (Fig. 52.6). Jin et al. reported one case of acute stroke in 200 patients treated with RFA, but this is likely unrelated to the ablation as this has not been reported in other series. Vaughn et al.

reported a case of massive hemorrhage in a 70-year-old man undergoing RFA of a lung malignancy due to concomitant clopidogrel. Clinically relevant bleeding is not common due to the coagulative effect of the ablation procedure.

The advantages of microwave ablation include consistently higher intratumoral temperatures, larger tumor ablation volumes, fast ablation times, use of multiple applicators, more effective heating of cystic masses, and improved convection profile. There is also increased affinity for water-based tissues and decreased "heat sink" effect. In addition, because microwave ablation does not rely on an electrical circuit as does RF ablation, multiple applicators can be applied simultaneously. It was demonstrated by Brace and colleagues in a swine model that microwave energy compared with RF energy is a more effective energy source for use in the lung.

The advantages of CA over RFA include larger tumor ablation volumes, ability to use multiple applicators, and less procedural pain. CA technique does not require the use of grounding pads, thereby eliminating the problem of grounding pad injuries. Other advantages are the ability to preserve collagenous and other structural cellular architecture in any frozen tissue and the ability to see lower attenuation ice as it covers a soft tissue mass during the freeze cycles. Theoretical problems with CA include bleeding, requiring additional maneuvers such as tract coagulation with fibrin glue.

Further research is being performed to identify the ideal tumor size, cell type, tumor morphology, and location. In addition, the appropriate imaging follow-up criteria and timing to accurately determine the treatment success have yet to be completely defined. In the future, further delineation of which thermal ablation technique is best for the various clinical scenarios should be performed. Additionally, new advances and emerging technology should be focused on greater ablation volume in shorter time periods with real-time monitoring of the treatment effects.

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Part IV

Thoracoscopy

Pleural Anatomy and Fluid Analysis

53

Y.C. Gary Lee

Introduction

Pleural effusions are common in clinical respiratory practices and are often difficult to diagnosis or manage. Over 3,000 patients per million population develop a pleural effusion each year. At least 60 pleural, pulmonary, and systemic conditions have been associated with the development of pleural effusions. Establishing the underlying cause often requires invasive procedures, from thoracentesis to percutaneous pleural biopsy and thoracoscopy – all of which carry risks.

A clear understanding of the basic anatomy of the pleural cavity, the principles of pathophysiology of pleural fluid formation, and the role (and limitations) of current pleural fluid tests is therefore essential for all practicing pulmonologists.

Pleural Anatomy

Gross Anatomy

The pleural mesothelia develop from the embryonic mesoderm and differentiate into the parietal and visceral pleura by the third week of gestation. By 9 weeks, the pleural cavity is separated from the pericardial cavity. The pleural cavities contain the visceral pleura, overlying the entire lung surface, and the parietal pleura, overlying the inner surface of the entire thoracic cage, including the mediastinum and diaphragm (Fig. 53.1). The two pleural membranes coalesce at the lung hila, where they are penetrated by the major airways and pulmonary vessels. Several structures (e.g., the hila and sometimes the great veins) acquire a double layer of parietal pleura in embryological development to form the pulmonary ligaments, which may contain lymphatics or vessels.

The pleural cavity refers to the space enclosed by the pleural membranes which in healthy states is approximately 10–20 μm across and contains 8–10 mL of fluid. The area of the entire pleura is estimated to be 2,000 cm^2 in an average adult male. In humans, the left and right pleural cavities are separated from each other and from the pericardial space. The visceral pleura covers the lung surface and extends deep within the interlobar fissures. The parietal pleura can be divided into the diaphragmatic, mediastinal, cervical, and costal pleura, Fig. 53.2. The parietal pleura may extend inferiorly beyond the costal surface, specifically at the right lower sternal region and at the posterior junction of ribs and vertebra bilaterally.

Blood Supply: Major, and at times fatal, bleeding is a known complication of pleural procedures – hence, understanding the blood supply of the pleura is important. The costal portion of the parietal pleura is supplied by the intercostal and internal mammary arteries. Contrary to conventional teaching that the intercostal arteries run inferiorly to the corresponding ribs, angiographic evidence shows that in the paravertebral regions these arteries often follow a variable course in the intercostal space not necessarily protected by the ribs. The intercostal arteries only consistently run parallel with the inferior margins of the ribs when the vessels reach the flanks. Elderly subjects often have more tortuous vessels and narrower rib spaces and are at risks of intercostal artery lacerations during pleural procedures. Percutaneous procedures, and thoracoscopic biopsies, should be performed as far away from paravertebral regions as possible.

The bronchial, upper diaphragmatic, internal mammary, and mediastinal arteries supply the mediastinal pleura; the subclavian artery supplies the cervical pleura, and the diaphragmatic pleura is supplied by the internal mammary artery and aorta, via posterior mediastinal and inferior phrenic arteries. Venous drainage follows arterial supply into the azygos vein and into the superior vena cava. The diaphragmatic

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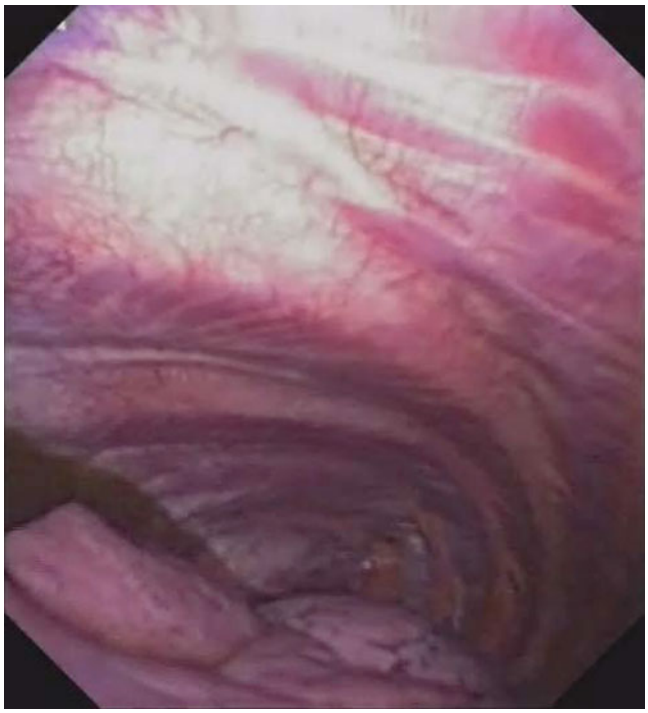

Fig. 53.1 Thoracoscopic view of the pleural cavity, looking toward the apex of the lung, showing the lung covered by visceral pleura (at *bottom* of the image) and the parietal pleura covering the inner surface of the ribs and chest wall

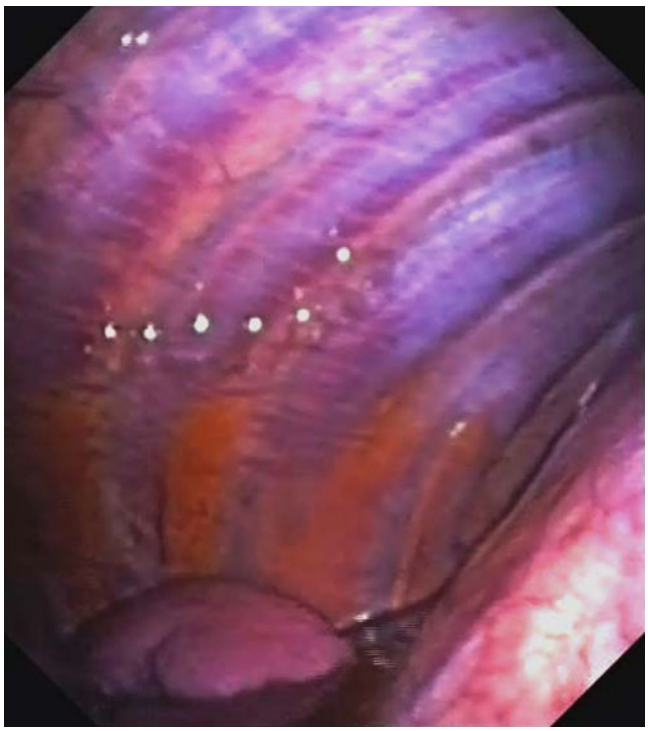

Fig. 53.2 Thoracoscopic view of normal costal parietal pleura. Normal pleura is extremely thin and offers a clear view of the underlying structures. Notice the ribs, and the intercostal vessels in between the ribs, running in parallel to each other. The diaphragm covered by the diaphragmatic pleura can be seen at the inferior *right corner* of the picture. A small amount of pleural fluid can be seen at the *bottom* of the pleural cavity

pleura drains via the inferior phrenic veins into the inferior vena cava.

Arterial supply of the visceral pleura in humans is believed to arise from the bronchial arteries, although supply of the lung apex and its convex surface is debated. Venous drainage of the visceral pleura is mostly via the pulmonary veins.

Pleural Lymphatics: The lymphatics play a key role in fluid drainage of the pleural cavity. Fluid exits the pleural cavity by bulk flow (liquid and protein are evacuated at the same rate) via stomata (diameter 2.5–10 μm) on the parietal pleura, which empty into lymphatic plexuses in the intercostal spaces and over the diaphragm. The costal pleura drains into the internal mammary nodes anteriorly and the intercostal lymph nodes posteriorly. Pleura from the lung apex drains into the cervical chain, while pleura lining the diaphragm drains into the mediastinal nodes. Disease, especially malignant, involvement of thoracic lymph nodes often impairs the drainage routes and contributes to accumulation of pleural effusions.

A superficial network of lymphatic capillaries and collecting vessels exists on the visceral pleura, and flow from lymphatic capillaries is directed toward the hila of the lung via bronchovascular bundles. Disruption of the lung and pleural lymphatics during lung transplantation is believed to be a contributing cause of the early posttransplant pleural effusions which occur in practically all lung transplant patients.

Innervation: The parietal, but not the visceral, pleura is innervated by pain fibers. Hence, presence of pleuritic pain indicates pathologic, usually inflammatory or tumor, involvement of the parietal pleura which is supplied by the intercostal nerves. The central diaphragm is supplied by the phrenic nerve; irritation of the diaphragmatic pleura can induce referred pain to the ipsilateral shoulder. The visceral pleura is innervated by the vagus and sympathetic trunk.

Microscopic Anatomy

Both visceral and parietal pleurae in humans are approximately 40 μm thick. Between the pleural surface and underlying tissue, five layers are identified histologically, consisting of a single cellular layer and four subcellular layers (Fig. 53.3), as follows:

1. A monolayer of mesothelial cells
2. The basal lamina and a thin connective tissue layer
3. A thin superficial elastic layer, often merged with the second layer
4. A loose connective tissue layer, containing nerves, blood vessels, and lymphatics
5. A deep fibroelastic layer, often fused to the underlying tissue

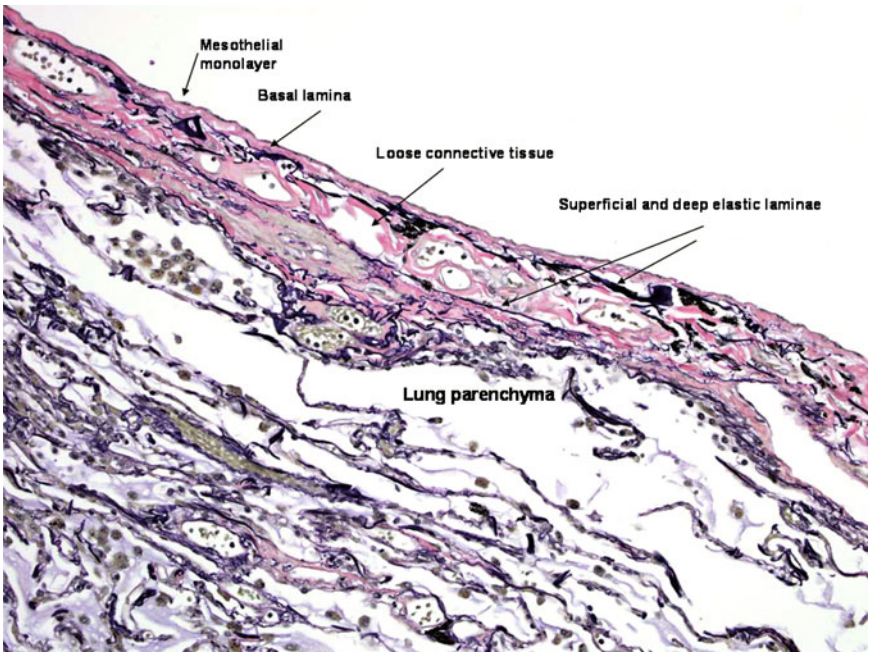

Fig. 53.3 The visceral pleura. The five layers of the visceral pleura, merging with underlying lung parenchyma. The elastic laminae of the pleura are highlighted in this Verhoeff-Van Gieson (VVG) stain for elastic fibers (VVG x 200) (Courtesy of Dr. A Segal, Perth, Australia)

Mesothelial Cells: Mesothelial cell is the predominant cell type in the pleural cavity. They vary from flat to cuboidal and can range from 10 to 50 μm in diameter and from 1 to >4 μm in thickness. Mesothelial cells are adherent to one another at the apical surface via tight junctions. At the basal surface, the cells are more loosely associated, although the basal portions are often seen to overlap. The cells slide over one another during the respiratory cycle, and therefore, at full inspiration the overlap disappears completely.

The pleural cavity is frequently invaded by undesirable agents, but the pleural cavity is not under close surveillance by polymorphonuclear cells. Mesothelial cells thus provide the frontline defense against invading cells (e.g., cancer), pathogens (e.g., bacteria), and particular matters (e.g., asbestos) by provoking a significant inflammatory response, phagocytosis, and release of potent cytokines which effectively recruit inflammatory cells (e.g., neutrophils) to initiate appropriate immune responses to eradicate the invading molecules. Mesothelial cells are multipotent and have definite roles in extracellular matrix synthesis and hence pleural fibrosis and repair. The diverse range of biological functions mesothelial cells play in both health and disease states is reviewed elsewhere.

Pathologic Changes in the Pleura

A diverse range of insults can affect the pleura, and the resultant responses are equally complex. Most pleural disorders, however, involve inflammatory changes, fibrosis, and often vascular hyperpermeability, leading to fluid accumulation. Detailed discussion on pleural pathologies can be found in specialist texts.

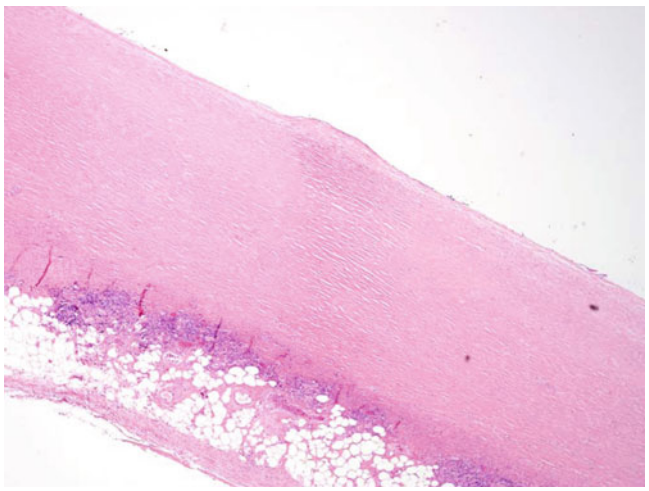

Fig. 53.4 Fibrous pleural plaque of the parietal pleura, demonstrating "basket-weave" collagen (H & E x40) (Courtesy of Dr. A Segal, Perth, Australia)

Pleural Inflammation and Fibrosis: Acute pleuritis develops with many pleural diseases (e.g., infection) as well as iatrogenic procedures (e.g., pleurodesis), and if persists, the chronic inflammation often progresses to pleural fibrosis and thickening (e.g., asbestos-related fibrothorax) (Fig. 53.4). In addition to fibroblasts, mesothelial cells also contribute to collagen and matrix synthesis in pleural fibrosis. Mesothelial

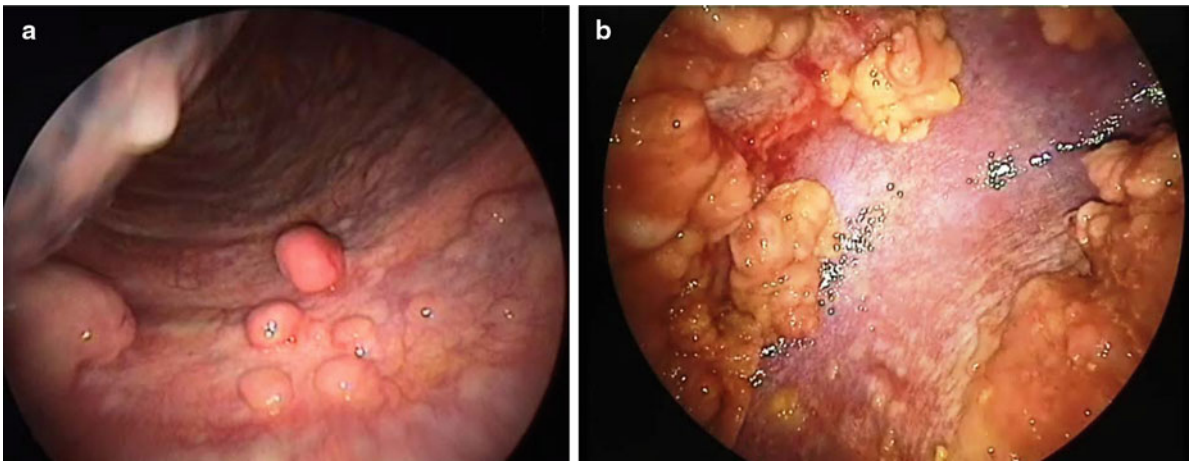

Fig. 53.5 Thoracoscopic views of (**a**) multiple metastatic carcinoma deposits on the parietal pleura and (**b**) malignant mesothelioma at the parietal pleura (*left*) and diaphragm (*right*) sparing the costophrenic angle (Courtesy Dr. N Rahman, Oxford, UK)

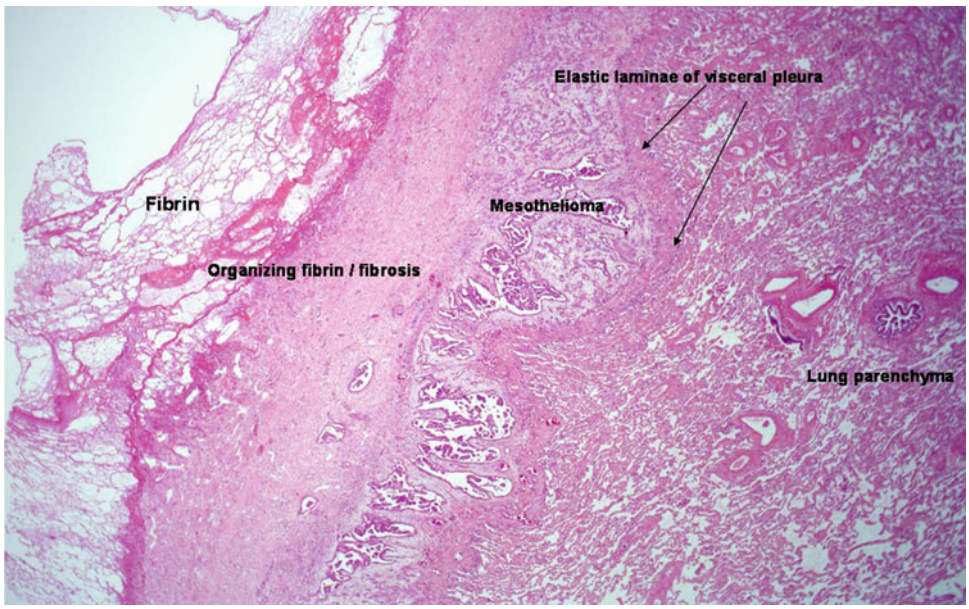

Fig. 53.6 Malignant mesothelioma, epithelioid type. A reactive zone of fibrin and fibrous tissue (*left*) overlies the tumor, which is separated from the underlying lung parenchyma by the elastic lamina of the visceral pleura (H & E x20) (Courtesy of Dr. A Segal, Perth, Australia)

cells can undergo epithelial-mesenchymal transformation and convert into fibroblast-like cells, a process implicated in peritoneal fibrosis. For detailed review of the causes and pathology of pleural fibrosis, please refer to reviews elsewhere.

Pleural Effusion: The development of pleural effusions is further discussed below.

Pleural Malignancy: An estimated 300,000 patients develop a malignant pleural effusion per annum in the USA, which can arise from metastatic or primary pleural cancers. Metastatic pleural disease accounts for the majority of cases (Fig. 53.5a) with lung and breast being the most common primary cancer sites. In Europe, one million patients with lung cancer develop a pleural effusion each year. Cancer cells embolize to peripheral lung tissues and/or directly invade the visceral pleura before spreading onto the parietal surface. Occasionally, hematogenous or direct spread to the parietal pleura can occur. In contrast, primary pleural mesothelioma (Fig. 53.5b) is believed to originate from the parietal pleura before spreading to the visceral pleura. Mesothelioma patients with disease limited to the parietal, but not the visceral, pleura have been shown to have better prognosis (33 vs. 7 months). Figure 53.6 shows an example of the histological appearance of a malignant pleural mesothelioma.

The importance of pleural involvement in non-small cell lung cancer has been recognized in the latest (7th edition) revised "TNM classification of malignant tumors"; the presence of a malignant pleural effusion staged the cancer at M1a (stage IV), reflecting the advanced (and inoperable) nature of the disease when the pleura is involved. A series of studies have shown that positive pleural lavage cytology for malignant cells is a poor prognostic indicator in patients undergoing resection of lung cancer, with a median survival of 13 months compared to 49 months if negative. The importance of pleural lavage cytology has recently been emphasized in a meta-analysis. Currently, results of pleural lavage are not part of the TNM staging system. However, a new classification of visceral pleural invasion (VPI), PL0-3, has been proposed and is now in use in many centers:

PL0: tumor within the subpleural parenchyma or invading superficially into the pleural connective tissue below the elastic layer;
PL1: tumor invades beyond the elastic layer;
PL2: tumor invades the visceral pleural surface;
PL3: tumor invades the parietal pleura.

Breaching the elastic layer of the visceral pleural layer, PL1 and 2, confers VPI and a T status of pT2. Five of the six studies using this staging system showed adverse prognosis for patients with VPI. Parietal involvement is termed pT3.

Pleural malignancies often express high levels of vascular endothelial growth factor (VEGF), which in animal studies is a key driving force for pleural/peritoneal fluid formation. The role of antagonizing VEGF to control malignant effusions has not been established.

Pneumothorax: Stretched out visceral pleura in the statically expanded lung apices is prone to bleb and bullae formation, even in nonsmoking individuals. These are thought to be an important factor in predisposition to primary spontaneous pneumothorax. A recent study of primary pneumothorax using fluorescein-enhanced autofluorescence thoracoscopy raises the possibility of diffuse leak from the visceral surface ("pleural porosity") rather than one ruptured bleb as the source of air leak from the lung.

Due to the anatomical boundaries of the parietal pleura, iatrogenic pneumothorax may result from insertion of subclavian central venous catheters, damaging the pleura above the first rib. Due to pleural extension below the costal margin inferiorly, pneumothorax may occur during attempted posterior access to upper abdominal organs.

Role of the Pleural Cavity

The pleura permits friction-free movement of the lungs within the relatively rigid thorax and facilitates the development of positive and negative intrapleural pressure during the respiratory cycle. A patent pleural cavity is, however, not essential to life. Longitudinal studies of patients who underwent talc pleurodesis to obliterate the pleural space as treatment for pneumothoraces showed minimal restrictive changes in lung functions after 22–35 years. This was collaborated by animal studies which showed no major impairment in lung volumes and gaseous exchange following pleurodesis. Studies of elephants showed that many were autopleurodesed at birth, and their pleural cavity is replaced by fibrous tissues. It is intriguing why humans, throughout evolution, maintain a patent pleural cavity that is nonessential and susceptible to numerous disease pathologies.

Pleural Fluid Formation and Absorption

In the healthy state, the pleural cavity contains a small amount of normal physiologic fluid to facilitate the gliding of the visceral pleura over the parietal pleural membrane. This pleural fluid is formed by filtration, according to the net hydrostatic-oncotic pressure gradient, from the systemic, especially the intercostal arterial, circulation of parietal pleura. Water and small molecules (≤4 nm) can pass freely between the mesothelial cells, whereas transcytosis can allow active transport of larger particles through the mesothelial cells.

There is approximately 0.13 ± 0.06 mL/kg body mass of normal physiologic fluid in each hemithorax as estimated by the urea dilution method in a pleural lavage study of normal subjects undergoing thoracoscopy. The fluid is a transudate with low protein and lactate dehydrogenase (LDH), and its biochemical composition (e.g., glucose and urea concentrations) resembles that of other interstitial fluids. Total leukocyte counts average 1,716 cells/μL, which are predominantly (75%) macrophages and lymphocytes (23%) in nonsmokers, but the numbers of neutrophils are significantly raised in smokers.

Extrapolating from animal data, a 70-kg man produces 17 mL/day of physiologic pleural fluid. The rate of formation approximates 0.01 (in sheep) to 0.02 (in rabbits) mL/kg/h, and the half-life of fluid turnover is 6–8 h. The drainage capacity in normal pleura is large (estimated around 0.2–0.3 mL/kg/h) and well over the usual production rates.

Pleural Fluid Formation in Pathologic States

A pleural effusion, an abnormal accumulation of pleural fluid, develops when the rate of pleural fluid formation exceeds the rate of its removal. Most effusions develop from both increases in pleural fluid entry and decreases in fluid exit rates. In the presence of the normal fluid absorption capacity, fluid formation has to increase by over 30-fold, and stay at that rate, to create an effusion. On the other hand, decreased removal of the fluid alone is unlikely to result in

significant accumulation of pleural fluid, given the normal rate of pleural fluid formation is low.

Transudates account for ~60% of pleural effusions seen in clinical series. They are formed when the Starling's equation is disturbed by increased intravascular pressures (most commonly in congestive cardiac failure) and/or decreased pleural fluid oncotic pressures (e.g., in cirrhosis and nephrotic syndrome): all of which can contribute to fluid movement across the pleural capillaries to the pleural cavity.

The pleural cavity acts as an escape route for interstitial fluids of the lung: ~20% of these fluid drains into the pleural space. Congestive cardiac failure is the most common cause of transudative pleural effusions. In pulmonary edema, the amount of interstitial fluid in the lung, and hence that exiting into the pleural cavity, rises significantly and can overwhelm the pleural drainage capacity, presenting as (most commonly) bilateral pleural effusions.

Increased pleural fluid formation also results from pleural inflammation. Exudates form as a result of vascular hyperpermeability, usually due to inflammation or injury to the vascular bed, or "leaky" tumor neovasculature. The resultant pleural fluids usually contain a high protein concentration relative to the transudates.

It should be remembered that pleural effusion can accumulate from passage of fluid from extrapleural sources, the most common being transdiaphragmatic movement of peritoneal fluid (e.g., ascites or dialysates). Other sources to consider include chyle from thoracic duct leak, infusion fluid from misplaced central venous lines, hemothorax from lacerated intrathoracic blood vessel, and other body fluids via fistulae (e.g., urinothorax).

Decreased pleural fluid absorption contributes to pleural effusion accumulation. This can occur if the parietal stomata are obstructed by inflamed or grossly thickened pleura, such as with pseudochylothorax, or when the downstream lymph nodes are involved in pathologic, e.g., tumor metastases, processes.

Physiologic Effects of Pleural Effusions

Dyspnea is the most common symptom associated with pleural effusions, but its pathophysiologic mechanism remains debated. Fluid compression on the lung, a common belief, is not the sole explanation as the forced vital capacity and the forced expiratory volume in 1 s (FEV_1) increases by about 200 mL for every liter of pleural fluid drained. The improvement in pulmonary function is greater in patients with higher initial pleural pressure. Not surprisingly, the arterial blood gas parameters (e.g., oxygen tension) do not improve significantly, and may even deteriorate, after thoracentesis as the intrapulmonary shunt underlying the hypoxemia does not change significantly.

To accommodate the extra volume (often in liters) of pleural fluid, the thoracic cavity has to expand (e.g., by mediastinal shift, flattening, or eversion of the hemidiaphragm). Indeed, the weight of the fluid on the diaphragm profoundly alters the hemidiaphragm shape and functioning. The patient whose hemidiaphragm is everted usually has severe dyspnea.

In animal studies, massive pleural fluid accumulation can raise the intrapleural pressure sufficiently to reduce venous return and thus cardiac output. This hypothesis has not been properly assessed in humans.

Pleural Fluid Analyses

General Principles

Establishing the diagnosis of a pleural effusion can be challenging. It should be emphasized that pleural fluid analyses should always be interpreted in conjunction with clinical history, examination, and radiologic assessment (*see other chapters*). For example, the British Thoracic Society pleural guidelines recommend that in "an appropriate clinical setting, e.g., left ventricular failure with a confirmatory chest radiograph, these effusions do not need to be sampled unless there are atypical features or they fail to respond to therapy." There are also no specific pleural fluid features that can clinch the etiology of many disorders – their diagnoses are made given the appropriate clinical background and a consistent biochemistry profile of the pleural fluid analyses. Common examples include drug-induced pleural effusions, effusions associated with pulmonary emboli, and benign asbestos pleuritis.

Direct Inspection of the Pleural Fluid

Inspection of pleural fluid is an important part of the assessment, often overlooked by clinicians. The presence of pus defines empyema at the bedside (Fig. 53.7), and finding of food particles defines a fistula connection with the gastrointestinal tract (usually esophagus). A milky fluid must raise the suspicion of chylothorax or pseudochylothorax and be differentiated from turbidity from bacterial infection. Pleural aspirates are often hemorrhagic, and most are results of blood staining of the fluid than a genuine hemothorax (Fig. 53.8) – the latter is defined by a fluid:blood hematocrit of >0.5. The smell of ammonia suggests urinothorax; an anaerobic smell in empyema helps guide antimicrobial choice.

Laboratory Tests of the Pleural Fluid

Laboratory tests should be requested as according to the clinical setting, and no "set menu" fits every patient. When approaching a undiagnosed effusion, however, the following

Fig. 53.7 Pus in chest tube and underwater-sealed bottle from a patient with empyema

Fig. 53.8 Hemorrhagic pleural effusion from a patient with known malignant pleural mesothelioma

tests are generally recommended: pleural fluid should be sent for protein and LDH, pH and/or glucose, differential leukocyte counts, bacterial culture, and cytology.

Differentiation Between Transudates and Exudates: Defining the effusion as a transudate or exudate is often useful in the workup of a undiagnosed pleural effusion and helps triage further investigations. Most commonly, differentiation between transudative and exudative effusions is made using Light's criteria. A pleural effusion is an exudate if it satisfies *any* of the following criteria. Conversely, a transudate is one that meets none of the criteria:

- Pleural fluid:serum protein ratio >0.5
- Pleural fluid LDH >2/3 of the upper limit of normal serum LDH
- Pleural fluid:serum LDH ratio >0.6

Transudative effusions result from imbalance of the hydrostatic and oncotic pressures, and the pleura itself is not directly involved in the pathogenesis. Investigations should be directed towards extrapleural causes, most commonly congestive cardiac failure, liver cirrhosis, or nephrotic syndrome. Exudates, on the other hand, point towards a pleural pathology, with parapneumonic, tuberculous, and malignant pleural effusions accounting for the majority of exudates.

Although generally robust, Light's criteria have many recognized limitations that clinicians must be aware of. In loculated effusions, clinically significant variations in fluid biochemistry have been demonstrated. Light's criteria are unable to inform clinicians in situations when exudative and transudative forces coexist. For example, ~8% of malignant effusions are transudates, presumably from concomitant cardiac failure or low protein states. Light's criteria are set to provide a high diagnostic sensitivity for exudates; false positives therefore can occur, e.g., patients with transudative effusions receiving diuretics may have protein values in the exudative range.

Numerous alternatives to Light's criteria have been proposed over the years; none has shown clear advantages. A growing number of disease-specific markers are being developed to establish the definitive diagnosis of pleural fluids and may eventually negate the need for triaging effusions as transudates and exudates.

Pleural Fluid Cytology: At least 50 mL of pleural fluid should be sent for cytologic analyses; several studies have shown that submitting larger amount of fluid does not increase the diagnostic yield of malignancy from cytologic examination. Presence of malignant cells in the pleural fluid defines a malignant effusion (Fig. 53.9). However, clinicians must acknowledge that the negative predictive value of pleural fluid cytology for malignancy is poor – limited by quality of samples, appearances of cells, experience of cytologists, etc. Certain malignancies, e.g., sarcomas, mesotheliomas, and lymphomas, are more difficult to be diagnosed by cytology. Further diagnostic tests, e.g., thoracoscopy (*see other chapters*), should be considered.

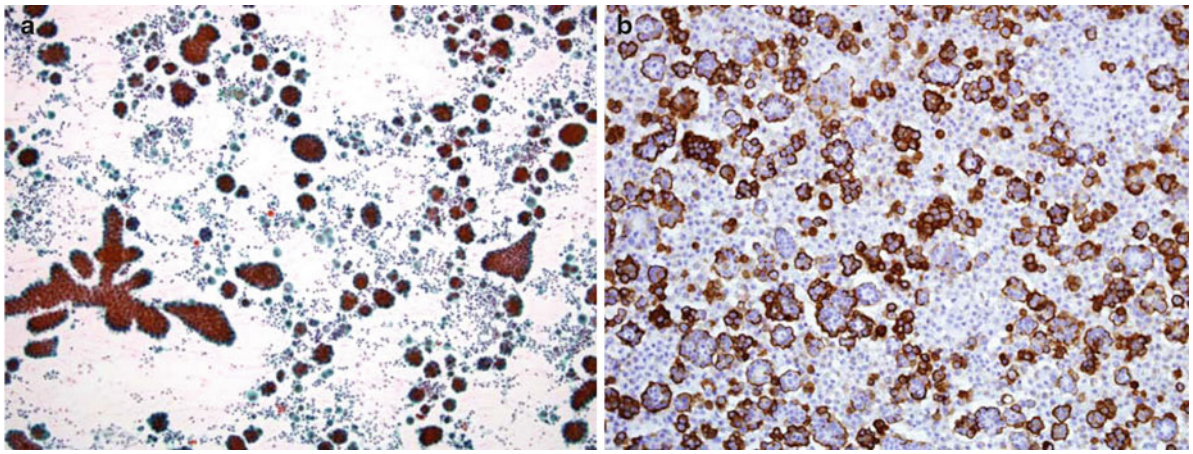

Fig. 53.9 Malignant mesothelioma cells in pleural fluid. *Left*: highly cellular sample containing large 3-dimensional clusters and papillary aggregates. *Right*: strong membranous staining for epithelial membrane (EMA) in most aggregates. EMA is positive in up to 85% of mesotheliomas in pleural effusion cytology and is useful for distinguishing benign from malignant effusions; further immunophenotyping is required to distinguish between mesothelioma and adenocarcinoma (Pap x100; EMA IPOX x200) (Courtesy of Dr. A Segal, Perth, Australia)

Pleural Fluid pH and Glucose: In parapneumonic effusions, low (<7.20) pleural fluid pH or glucose (<40 mg/dL) is predictive of the need for chest tube drainage. This pH cutoff has been used in many large clinical studies to define "*pleural infection*" – a composite term comprising complicated parapneumonic effusion and empyema. Although glucose is usually low in pleural infection and correlates to pleural fluid pH values, it is a less accurate indicator for chest tube drainage when compared to pH.

Low pleural fluid pH and glucose reflect high metabolic activities in malignant pleural effusions, and low pH has been associated with poorer prognosis and is (weakly) predictive of unsuccessful talc pleurodesis. Pleural fluid acidosis (pH < 7.30) can also occur in connective tissue diseases (particularly rheumatoid arthritis), tuberculous pleural effusions, and esophageal rupture, and in isolation, it does not distinguish between these causes. Low pleural fluid glucose (<29 mg/dL) is common in pleural effusions secondary to rheumatoid arthritis.

The accuracy of pleural fluid pH assessment is critically dependent on the collection and measurement methods. Fluid should be collected in a blood gas syringe without presence of air (which increases pH by an average of 0.08) or carry-over lidocaine (which is acidic and significantly reduces pH) and be measured in a blood gas machine (not pH meters or papers), preferably within 1 h of collection. As such, pleural fluid glucose is employed in some centers as an alternative.

Pleural Fluid Leukocyte Counts: Differential pleural fluid white cell counts can help direct investigations. Neutrophilic pleural fluids suggest intense pleural inflammation and are commonly associated with parapneumonic effusion/empyema, pulmonary emboli, pancreatic effusions, and malignancy.

Lymphocytic (lymphocyte >50% of total leukocytes) pleural fluids may suggest TB, malignancy, post-coronary artery bypass (CABG) effusion, chronic rheumatoid pleuritis, or lymphatic disruption (lymphoma, chylothorax, yellow nail syndrome).

Eosinophilic (eosinophils >10% of total leukocytes) pleural effusions are secondary usually to blood or air in the pleural space. It can also be associated with a range of diseases, including post-coronary artery bypass graft pleural effusions, benign asbestos pleural effusions, Churg-Strauss syndrome, lymphoma, pulmonary infarct, parasitic/fungal infections, and allergic reactions (especially drug-induced pleuritis). In one series of 60 eosinophilic effusions, 37% were of malignant etiologies.

Bacterial Culture: No organisms were detected in up to 40% of patients with pleural infection in many studies; thus, the absence of positive bacterial culture does not exclude the diagnosis. Inoculating pleural fluid into blood culture bottles increases the sensitivity of culturing microbes than using plain containers for transportation. Blood culture should be performed in patients suspected of empyema to increase the likelihood of capturing the infective organism.

Other Pleural Fluid Tests

A wide range of other tests can be performed on pleural fluids if clinically appropriate, but their routine use in pleural fluid assessment is not indicated.

TB Pleural Effusions and Adenosine Deaminase: TB is one of the most common causes of exudative effusions in

endemic countries. TB pleuritis is a type IV hypersensitivity reaction to mycobacterial proteins, and the amount of acid-fast bacilli in the pleural space is often very low. Pleural fluid culture therefore has very low (10–20%) yield for TB, as is culture of biopsied pleural tissue. TB pleural fluid is an exudate and most commonly (93% of cases) lymphocytic. The diagnosis is usually established by finding caseating granulomata in pleural tissue. This involves either percutaneous or thoracoscopic biopsies, and thus, a large amount of research has focused on the search of surrogate biochemical markers.

Adenosine deaminase (ADA) is now routinely used in many endemic countries for the diagnosis of TB pleuritis. A high level of this lymphocyte enzyme is very suggestive of TB, though false positives can occur with empyema (which can easily be separated on clinical grounds and a neutrophilic rather than lymphocytic effusion), lymphoma or metastatic malignancies, and rheumatologic causes. A recent meta-analysis of 63 studies confirmed a high sensitivity and specificity of 92% and 90%, respectively. Restricting the testing to only lymphocytic effusions will further enhance the accuracy of the test. Although the use of ADA isoenzymes may improve the performance of the test, they are expensive and technically more difficult to perform – thus limiting their utility in developing nations.

ADA is cheap, fast, and easy to measure and remains useful in HIV or immunosuppressed (e.g., renal transplant) hosts. In endemic countries, a high pleural fluid ADA in a patient with compatible clinical picture is considered sufficient to commence antituberculous treatment. A low ADA is a useful "rule out" test of TB pleuritis in regions with low disease prevalences.

Unstimulated interferon-gamma levels in pleural fluid have similar diagnostic accuracy as ADA but are more expensive. Interferon-gamma-releasing assays have been studied but failed to show sufficient clinical value in defining TB pleural effusions.

Cardiac Failure and N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP): The proBNP is released from cardiac myocytes upon mechanical stretching to "protect" the heart by inducing diuresis. ProBNP is cleaved to yield NT-proBNP and BNP molecules. NT-proBNP has been shown in several series, Table 53.1, to be effective in discriminating transudates associated with congestive heart failure (CHF) from other transudative or exudative causes. The most common cutoff value used was 1,500 pg/mL. Importantly, NT-proBNP correctly diagnoses CHF as a cause of most effusions that have been misclassified as exudates by Light's criteria. Few studies have compared pleural fluid versus blood NT-proBNP, or pleural fluid NT-proBNP versus BNP in their diagnostic value.

Tumor Markers in Pleural Fluid: Generally speaking, tumor markers and cytokine levels in pleural fluid are neither sensitive nor specific enough for diagnostic purposes despite a large volume of publications assessing their clinical utility. For example, a panel of pleural fluid tumor markers including CEA, CA-125, CA 15–3, and CYFRA 21–1 reached a combined sensitivity of only 54% (if specificity is set at 100%) for the diagnosis of malignancy.

Table 53.1 Recent large series published using pleural fluid NT-proBNP level to diagnose pleural effusion from congestive heart failure (CHF). "N" denotes the total number of patients in the series; (CHF case) denotes the number of patients with CHF in the study. The right hand column indicates the number of CHF effusion incorrectly labeled as exudate by Light's criteria that are correctly diagnosed using NT-proBNP (Modified from Hooper et al.)

	N = (CHF case)	Sensitivity (%): specificity (%)	Correct in samples misclassified (Light's criteria)
Han et al. Intern Med 2008	n = 240 (82)	95: 99	96% (n = 27)
Porcel et al. Chest 2009	n = 181 (90)	96: 88	90% (n = 18)
Porcel et al. Am J Med 2004	n = 117 (44)	91: 93	80% (n = 8)
Porcel et al. Respirology 2007	n = 93 (53)	92: 87	75% (n = 6)
Kolditz et al. ERJ 2006	n = 93 (25)	92: 93	100% (n = 5)
Liao et al. Respirology 2008	n = 40 (10)	100: 97	N/A

Malignant mesothelioma is often difficult to diagnose because of its relatively nonspecific initial presentations and the long lag time between exposure and disease development. Developing new (blood and/or pleural fluid) biomarkers for early detection of mesothelioma is an active area of pleural research. No molecule yet sufficiently identifies all subtypes of mesothelioma or differentiates it from other pleural malignancy or benign conditions. The most studied markers of mesothelioma are mesothelin and osteopontin.

Mesothelin is a new FDA-approved biomarker for mesothelioma. It is a differentiation protein found on the surface of mesothelial cells in serosal cavities. It is overexpressed in epithelioid and biphasic mesotheliomas and in some other tumors, particularly ovarian and pancreatic carcinomas. Significantly higher levels are detected in the serum of patients with mesothelioma-related pleural effusion, compared to patients with an effusion secondary to other cancers or benign pleural disease and to normal controls (diagnostic sensitivity 80–84% and specificity 83–100% for mesothelioma). Sarcomatoid mesothelioma often does not overexpress mesothelin, thus limiting the negative predictive value of the assay. Serum mesothelin levels are higher in patients with a larger tumor load, and its role in disease prognosis and monitoring treatment response is being explored. Mesothelin is renally excreted, and patients with kidney failure can have elevated blood levels.

Pleural fluid mesothelin levels correlate strongly with, and are much (~20×) higher than, those in corresponding serum. The reported diagnostic sensitivity and specificity for mesothelioma are between 71–80% and 83–89%, respectively (at a cutoff of 20nM). A recent study confirms additional value of pleural fluid mesothelin to conventional cytologic examination for mesothelioma, particularly in cases where the histocytology was highly suspicious but not definitive.

Megakaryocyte-potentiating factor (MPF) is derived from the proteolytic fragmentation of the mesothelin precursor protein; its role remains unclear. A recent study by Hollevoet et al. demonstrated a diagnostic sensitivity and specificity of serum MPF, at a cutoff of 12.38 ng/ml, of 68% and 95%, respectively, for the differentiation of patients with mesothelioma from healthy controls and other subjects who were either asbestos-exposed, had underlying benign asbestos-related or other respiratory disease, or lung cancer.

Pass et al. showed that serum osteopontin levels were significantly higher in patients with mesothelioma than in asbestos-exposed people without mesothelioma (diagnostic sensitivity and specificity 77.6% and 85.5%, respectively). However, high osteopontin levels are also recognized in lung, breast, gastrointestinal, and ovarian carcinomas; and osteopontin poorly discriminates patients with metastatic pleural disease from patients with mesothelioma-related pleural effusion. Its role in predicting prognosis and in monitoring therapeutic response is being studied.

Although mesothelin has a greater diagnostic accuracy than other tumor markers, its real clinical utility in the investigation of a undiagnosed pleural effusion, particularly in combination with routine clinical and radiological assessment, warrants further study before its use can be routinely recommended.

Pleural Fluid Amylase: High pleural fluid amylase can occur with esophageal rupture, in effusions due to pancreatic causes (e.g., from pancreatic pseudocysts), and in about 10% of malignant (especially adenocarcinomas) pleural effusions. In esophageal rupture, it is the salivary amylase that is elevated, whereas pancreatic amylase is raised with pancreatic diseases. However, routine measurements of pleural fluid amylase (or its isoenzymes) are not indicated.

Lipid Analyses: If the fluid appears milky, it should be examined for chylomicrons and triglyceride (found in chylothorax) and for cholesterol levels and cholesterol crystals (found in pseudochylothorax). It should be remembered that chylothorax may not look milky if the patient is starved. Triglyceride levels of 110 mg/dL in pleural fluids are usually diagnostic of chylothorax, though a level of 55–110 mg/dL is still consistent of the diagnosis. Pleural effusion from pseudochylothorax usually has a cholesterol level of over 200 mg/dL.

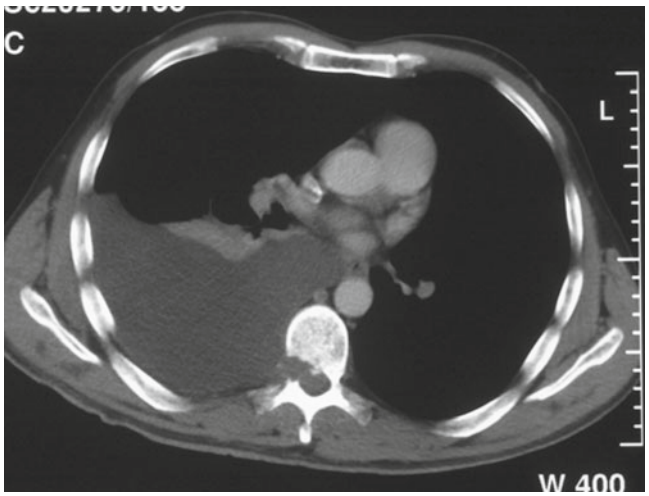

Fig. 53.10 A 44-year-old man had T7/8 discectomy and developed a postoperative pleural effusion, which on CT scan was continuous with the subarachnoid space. The fluid was positive for beta-2 transferrin, confirming the fluid originated from cerebrospinal fluid (Adapted with permission from Menzies SM and Griffiths SJ, Int Pleural Newsltr 2008; 6:19)

Flow Cytometry: Flow cytometry is very useful to diagnose lymphoma in effusions that are predominantly lymphocytic.

Beta-2 Transferrin: Diagnosis of a duropleural fistula can be made by the presence of beta-2 transferrin, a protein found in cerebrospinal fluid but not in normal pleural fluid (Fig. 53.10).

Connective Tissue Diseases and Autoimmune Antibodies: No diagnostic pleural fluid assessment can determine if a pleural effusion is associated with connective tissue disorders. Rheumatoid factor (RA) and antinuclear antibodies (ANA) can be raised in pleural fluid in patients with rheumatoid arthritis and SLE, respectively, but neither was specific. Pleural fluid RA and ANA levels are strongly correlated to the corresponding serum measurements, thus contributing little additional value in diagnosis.

Summary

Pleural diseases are diagnostic and management challenges commonly encountered in a pulmonologist's day-to-day practice. Knowledge of the basic pleural anatomy in health and disease states helps understand the pathogenesis. Pleural fluid examination is key to diagnosis of pleural effusions. New diagnostic markers continue to be developed and help to reduce the need of more invasive interventions. The future aim should be to develop more disease-specific markers that can identify the underlying pathophysiology or diagnosis.

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Pleural Imaging

54

Fergus Gleeson

Introduction

Imaging is now an essential and integrated component of both the diagnosis and management of pleural disease. This chapter focuses on the contribution of imaging to pleural disease and discusses the role of the different techniques including chest radiography (CXR), ultrasound (US), multislice computed tomography (MSCT), magnetic resonance imaging (MRI), and positron emission tomography combined with CT (PET-CT).

Techniques

Chest Radiography

An erect posterior-anterior (PA) radiograph (CXR) is almost invariably the first investigation performed in patients with known or suspected pleural disease. The use of the lateral CXR and decubitus films is now less common due to the use of US and MSCT. Erect and supine anterior-posterior (AP) radiographs are performed in patients unable to stand for a PA CXR but are less sensitive in the detection of small volumes of air or fluid.

Ultrasound

US is becoming ubiquitous in the management of pleural disease, being relatively portable, easy to use, and now commonly performed by clinicians at the time of consultation in clinic, emergency departments, and on the wards. Providing an adequate training program is in place, physician performed US for the detection of pleural fluid, and thoracocentesis has been shown to be as safe and diagnostically accurate as US performed by radiologists. It may confirm or refute the presence of an effusion, aid the differentiation between transudative and exudative effusions, demonstrate septations and/or loculations, detect malignant pleural disease, guide biopsy and drainage, and be used in the detection of a pneumothorax. A small footprint probe allows for intercostal access; high-frequency linear array transducers (7.5–12 MHz) provide the greatest spatial resolution but have limited penetration in larger patients and in patients with large volume pleural effusions. The compromise of a variable frequency (3.5–5.0 MHz) sector transducer provides adequate images and can be used to guide interventional procedures.

Multislice Computed Tomography

MSCT is now commonly used in the investigation and management of patients with pleural disease; it is more sensitive and specific in characterizing pleural thickening detected on CXR than US and may also be of value in patients with pleural effusions and pneumothorax. It should be performed using intravenous contrast with a delay of 60–90 s to optimize pleural enhancement, the tissue enhancement phase, rather than with dynamic contrast enhancement – vascular phase imaging and volumetric acquisition should be performed to enable multiplanar reconstruction.

Magnetic Resonance Imaging

MRI continues to have only a limited role in the investigation of pleural disease, due to its cost, relative lack of availability, and the excellence of the alternative techniques available. It may be used in the assessment of pleural malignancy and of extrapleural extension in patients allergic to iodinated intravenous contrast or if radiation exposure is to be avoided.

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A body coil should be used to obtain large field-of-view scout images, with specialized coils used for dedicated images. There are no prescriptive imaging sequences, as these should be tailored to the individual examination but typically include T1-weighted (T1W) images, which provide contrast between abnormalities in the pleural space and extrapleural fat; T2-weighted (T2W) images, which provide more tissue-specific information; and T1 post-intravenous gadolinium images, frequently performed post-fat saturation (FST1PG), which may be used to detect pleural enhancement present in malignant and infectious pleural disease. Dynamic contrast-enhanced MRI (dceMRI) has been used to assess angiogenesis and malignant pleural vascularity and to predict response to chemotherapy, although this remains a research tool. Real-time imaging has been used to assess chest wall compliance.

Positron Emission Tomography Combined with CT (PET-CT)

Coregistration of PET and CT using combined scanners has revolutionized the use of PET imaging, although its cost, limited availability, and length of examination times compared with other modalities have limited its use even in the assessment of malignant pleural disease. 18-Fluorodeoxyglucose (^{18}FDG) PET-CT is currently the only radioisotope that has been shown to be clinically useful in the investigation of pleural malignancy, although other radioisotopes and ligands are currently being investigated to assess cellular proliferation, tumor hypoxia, and angiogenesis. Malignant cells concentrate ^{18}FDG more avidly than normal tissue, and the consequent increased positron emission enables the detection and differentiation of malignant from benign disease with a relatively high sensitivity and specificity.

Anatomy

The normal pleura is comprised of two thin layers that form the boundaries of the pleural space. The visceral pleura lines and is inseparable from the surface of the lung, invaginating between the lobes to form the interlobar fissures. The parietal pleura abuts the extrapleural fat and endothoracic fascia of the chest wall and extends onto the mediastinal and diaphragmatic surfaces but is absent at the hila. The pleural surfaces of the two lungs oppose each other in the midline anteriorly and posteriorly, separated by the visceral and parietal layers of each lung and a variable amount of mediastinal fat (Fig. 54.1). Anteriorly, between the manubrium sternum and the base of the heart, the four layers condense to form the anterior junction line, which may be seen as a thin linear opacity extending from the sternal notch to the cardiac silhouette inferiorly, 1–3 mm thick, identifiable in up to 60% of PA CXRs, and on all MSCT scans. Posteriorly, the lungs may be opposed between the esophagus and upper thoracic vertebral bodies, to form the posterior junction line, extending from the lung apices to the aortic arch, usually 3–5 mm thick and identifiable in up to 30% of PA CXRs, and all MSCT scans.

There are two types of fissure: standard (oblique and horizontal) and accessory. Standard (interlobar) fissures vary

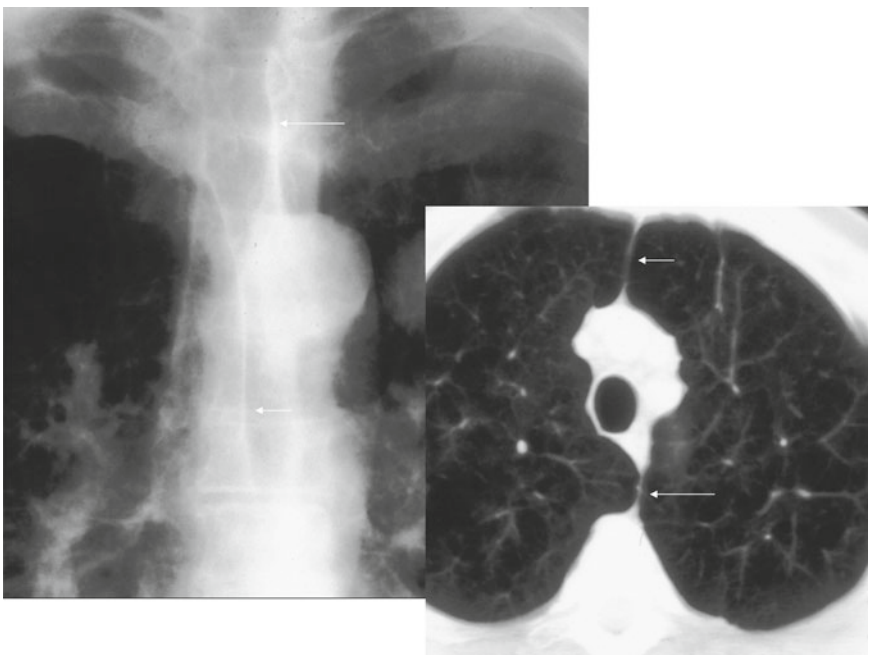

Fig. 54.1 Localized view of the junction lines on a CXR close up and associated CT. The anterior junction line (*short arrows*) is seen anterior to the mediastinum and does not pass up into the neck. The posterior junction line (*long arrows*) is seen posterior to the mediastinum and passes more cranial to the anterior junction lung

from complete lobar separation to incomplete, occasionally being only a few centimeters in length. Alterations in the course and position of these fissures may be suggestive of underlying pleural or parenchymal disease. The fissures are identifiable on all MSCT scans; the horizontal fissure, separating the right upper from middle lobe, is seen on PA and lateral CXRs, but the oblique fissures are normally only seen on a lateral CXR. Any pulmonary segment may be partially or completely separated from adjacent segments by accessory fissures, uncommonly identified on a PA CXR, but identifiable in up to 20% of CT scans.

Pneumothorax

The presence of gas between the visceral and parietal pleura, a pneumothorax, is always abnormal. Identification of the thin linear visceral pleura with absent lung markings beyond it and increased peripheral radiolucency are the primary radiographic signs but may not always be visible on CXR dependent on the quality of the radiograph and the size of the pneumothorax (Fig. 54.2).

Small pneumothoraces are less readily detected on supine or poor quality AP CXRs and in patients with severe pulmonary disease such as bullous emphysema (Fig. 54.3) or confounding radiographic abnormalities such as surgical emphysema. The detection of even small pneumothoraces may in these patients be critical, as they may be the cause of substantial respiratory impairment. On a supine CXR, the presence of a clearly marginated, well-defined hemidiaphragm is suggestive of a pneumothorax, because the gas collects anteriorly in a nondependent position and delineates the anterior aspect of the diaphragm. Detection may be helped by the presence of adjacent collapsed or consolidated lung, allowing the pneumothorax to be more readily detected, but in patients only suitable for supine CXRs a high index of suspicion is required to review the area adjacent to the diaphragm. Expiratory CXRs were previously advocated for the detection of small pneumothoraces but have been shown to add little to the diagnostic yield and are no longer recommended. Lateral CXRs were also previously performed to aid diagnosis, as were lateral decubitus views, particularly in emergency departments and in ICUs, but the use of US and/or CT has for the most part decreased the use of these views.

Larger volume pneumothoraces are more easily detected on PA, AP, and supine CXRs and may be of sufficient size to cause complete pulmonary collapse, mediastinal shift if under tension, and the deep sulcus sign in supine patients, with the lateral costophrenic recess seen more caudal than is usually apparent and of decreased radiolucency (Fig. 54.4).

Extrapleural artifacts such as skin folds, normal anatomic structures (companion shadows at the apex and medial edge of the scapula), breathing apparatus (oxygen reservoir bag),

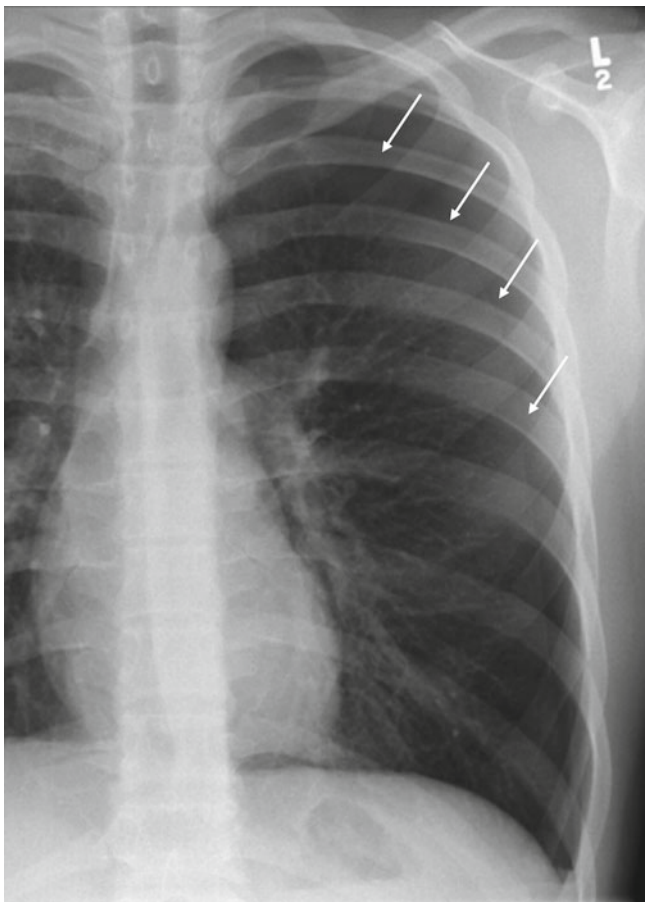

Fig. 54.2 Easily identified pneumothorax, with visceral pleural surface *arrowed*

and other lines, tubes, and wrinkles in clothing or bedsheets are common pitfalls that mimic the visceral pleural edge of a pneumothorax and should be positively excluded as the cause of a possible visceral pleural line (Fig. 54.5); external objects are easily recognizable if they have nonanatomical boundaries and extend beyond the thorax. Skin fold artifacts often manifest as a nonanatomical black line with fading margins, as opposed to the continuous white visceral edge of a pneumothorax, and vascular markings should also be traceable beyond a skin fold, but should terminate at the visceral edge of a genuine pneumothorax.

More recently, US has been shown to be of value in the detection of pneumothorax and is being increasingly used for their detection clinically, although patients with emphysema or bullous lung disease may be less easily assessed. It may also be difficult in trauma patients with surgical emphysema and may be false negative in patients with loculated pneumothoraces. MSCT is the gold standard in the detection and quantification of a pneumothorax, precisely reflecting pneumothorax size, permitting evaluation of underlying disease (such as emphysema, asthma, cystic fibrosis, and interstitial lung disease), and differentiating large bullae from a

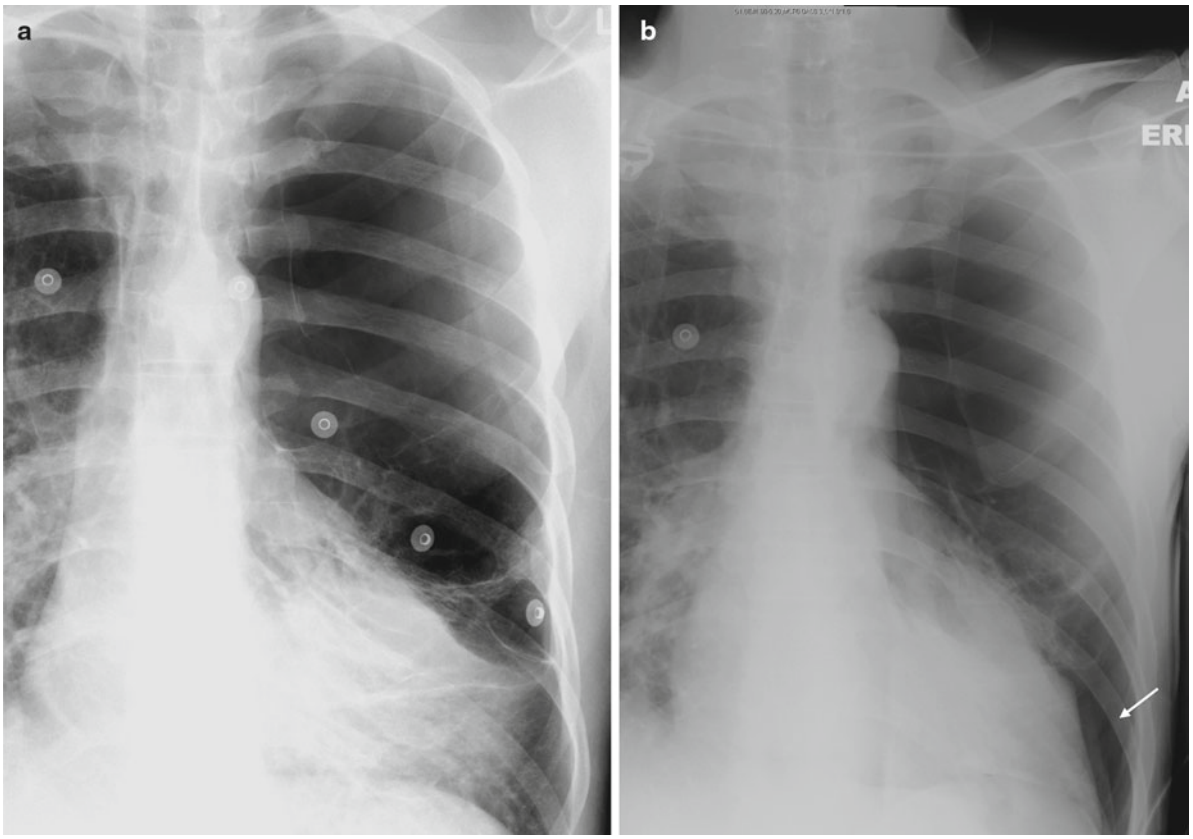

Fig. 54.3 (**a**, **b**) The initial CXR demonstrates bullous lung disease on the left, but lung markings are seen at the base. The second CXR shows absent lung markings confirming a pneumothorax

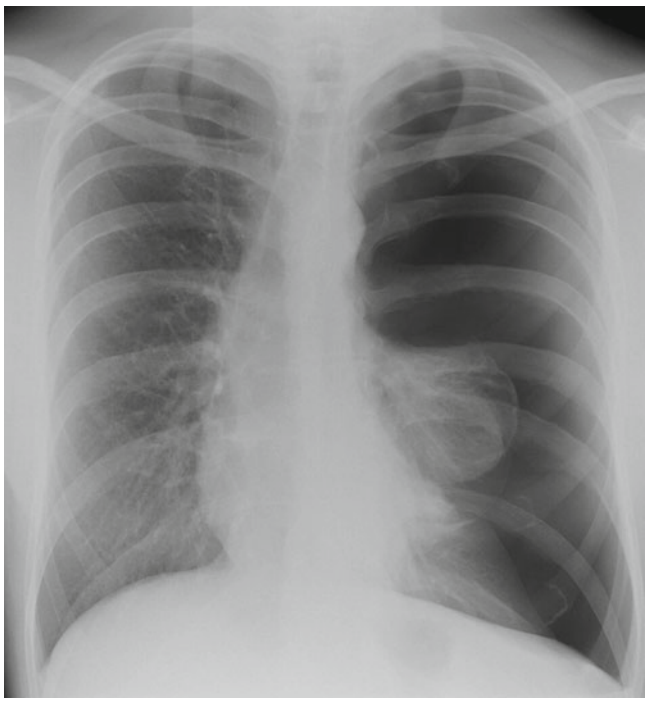

Fig. 54.4 A large left-sided pneumothorax demonstrating mediastinal shift and the deep sulcus sign

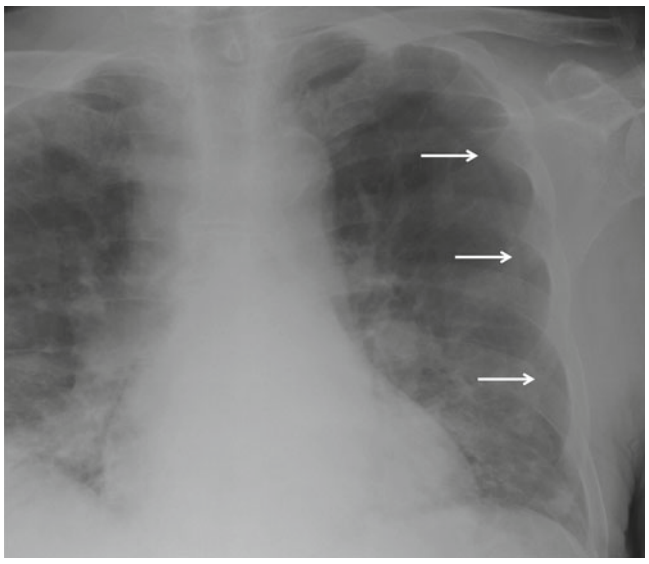

Fig. 54.5 An AP supine CXR demonstrating a pseudopneumothorax, due to a skin flap (*arrows*). This was confirmed on a subsequent image

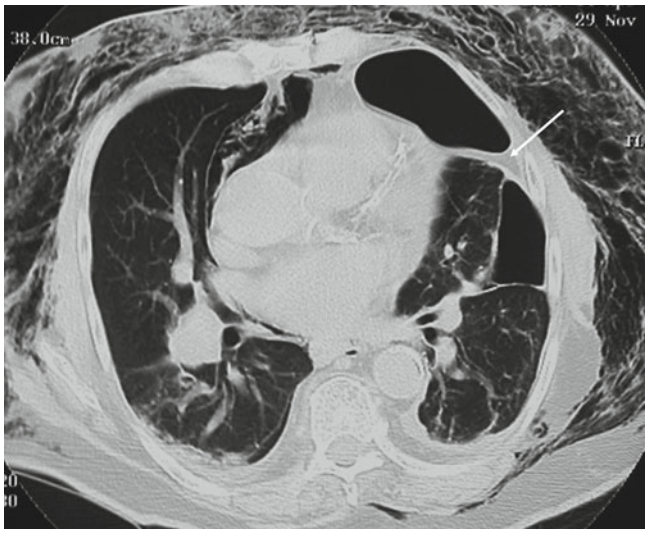

Fig. 54.6 Marked surgical emphysema prevented this left pneumothorax from being visible on the CXR. An *arrow* highlights the pleural adhesion that was also not visible

pneumothorax, although it may on occasion be difficult to interpret in some of these patients. It is also of value if associated surgical emphysema complicates radiographic interpretation. MSCT also identifies the presence of "tethered lung" adherent to chest wall and is the most valuable technique for guiding interventions in complicated cases and assessment of potentially malpositioned drains (Fig. 54.6).

Although there are some suggested methods of deriving approximations of "percentage" volume from the CXR, these are not of additional clinical benefit to subjective (small or large) estimates or a single objective distance of maximum visceral pleural separation to describe interval change. Published guidelines have provided some simple rules; a >2 cm rim of air on an erect CXR is classified as a large pneumothorax and <2 cm as small; or an apex to cupola distance >3 cm as large and <3 cm as small.

Pleural Effusion

The normal volume of pleural fluid present in a healthy adult, 0.1–0.2 ml/kg, is not detectable by imaging, so when identified, is always secondary to either local or systemic disease. Pleural effusion may be either due to increased formation, decreased reabsorption, or a combination of both. The majority of clinically important pleural effusions result from cardiac failure, infection, and malignancy, although other diseases such as pulmonary embolic disease may only be suspected because of the presence of an effusion. The differentiation of transudates from exudates although broadly possible using imaging techniques is guided by fluid biochemical profile. The effusion appearance is highly dependent upon patient position, its underlying etiology, and the age or stage of its evolution. As described earlier, the CXR is usually the initial assessment and may be all that is required or performed in patients with known disease, for instance, cardiac failure. Further investigation and management is most commonly by US with CT and more complex imaging tests performed if needed following on from US. The detection of pleural effusions in supine and ICU films may be difficult with even moderate-sized effusions missed or misdiagnosed, and US plays a key role in these patients. It is often helpful to either tilt the patient into a slightly seated or erect position if possible, or to roll them away from the side being examined to help gain access more posteriorly with the ultrasound transducer. It is critical to take time and if necessary have help when performing an US on ICU to enable the examination to be performed adequately. Under these circumstances, US may help confirm the presence of an effusion and also aid in the decision on the need for thoracocentesis and/or drain insertion. US can confirm the presence of very small volumes of fluid and may help to differentiate between transudates and exudates. While the majority of pleural collections can be managed using radiography and US, MSCT is of particular benefit in pleural effusions of undiagnosed etiology, having the ability to evaluate pleural morphology, underlying lung parenchyma and identify other sites of disease and other etiologic causes. MRI is of limited additional benefit, although, similarly to US, it may exquisitely demonstrate pleural nodularity or thickening, and septations or loculations.

An erect PA image reliably demonstrates fluid volumes only when they are in excess of 200 ml, with the typical appearance being homogeneous lower zone opacity with a well-defined curvilinear lateral meniscus. A standard lateral film may demonstrate blunting of the posterior costophrenic sulcus when at least 25–50 ml of fluid is present. The most sensitive CXR technique for very small effusions is a lateral decubitus image, demonstrating as little as 5–10 ml fluid. In the supine position, fluid layers posteriorly and may be difficult to detect on a supine CXR. Positive signs on supine or semierect images include an indistinct hemidiaphragm or blunting of the costophrenic angle; an increase in radioopacification of the hemithorax not obscuring the pulmonary vessels seen through it (Fig. 54.7); an "apical cap," as the apical region may be the most dependent in the supine position; and fissural thickening. In the erect position, fluid preferentially accumulates between the inferior surface of the lung and hemidiaphragm, filling the costophrenic sulci, from posterior to anterior, resulting in an increase in radiographic density below the diaphragm on a PA and AP CXR before tracking up the convexity of the lung to blunt the costophrenic recess. Occasionally, the effusion accumulates only in a "subpulmonic" location and may be difficult to identify, although comparison with prior or sequential films may be helpful.

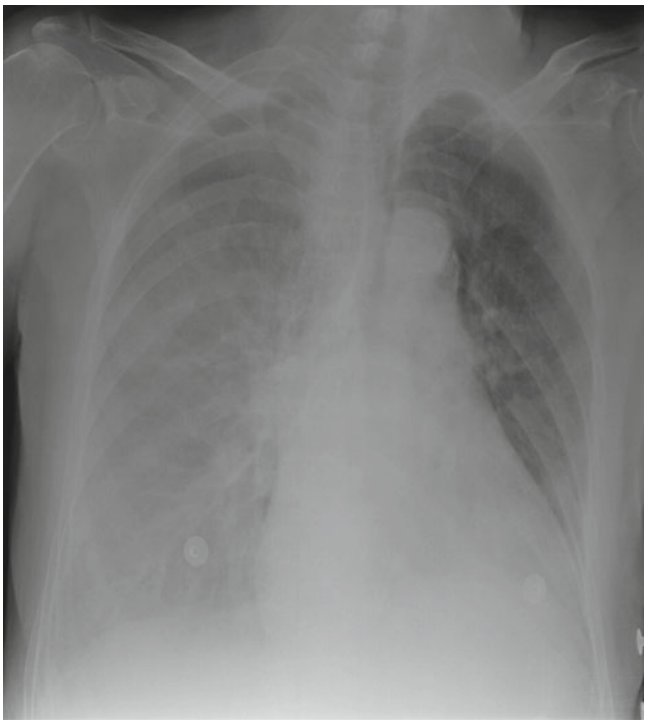

Fig. 54.7 A right-sided pleural effusion on a supine CXR, clearly demonstrated as an increase in radio-opacification of the hemithorax, but with the pulmonary vessels clearly seen through it

The CXR appearances include the apparent elevation of the hemidiaphragm with a lateral shift of the apex, the cupola of the diaphragm, and a poorly defined costophrenic angle; absent bronchovascular markings; and a gastric air bubble >1.0 cm below the "presumed" hemidiaphragm. Pleural fluid extending into the fissures produces variable appearances often rapidly changing on sequential imaging, depending on the location and overall volume of fluid at the time of the CXR. Fluid in the oblique fissure usually causes a faint curvilinear opacity on frontal radiographs, which is commonly sharpest medially and fades away superiorly and laterally.

On US, fluid is of variable echogenicity. Transudates are most commonly anechoic but have recently been shown to occasionally demonstrate septations. Exudative effusions are of variable echogenicity. The US appearances may sometimes help to distinguish between etiologies, although anechoic effusions may very occasionally yield frank pus on aspiration. Fibrin strands and septae are commonly present in exudates, and these are easily seen on ultrasound and are usually associated with infected or malignant collections. They may be so profuse as to have a honeycomb appearance. Other signs of an effusion on US include a dynamic "flap" or "swirl" induced by respiratory or cardiac motion and caused by atelectatic and consolidated lung, or debris and septations. Malignant effusions more often have a positive swirling sign than benign disease, but this sign is not sensitive or specific enough for diagnostic purposes. Pleural thickening can be difficult to distinguish from pleural fluid, as both may be anechoic or only faintly hyperechoic. Color Doppler US may help to differentiate fluid from pleural thickening if there is doubt, as movement in fluid induced by respiratory or cardiac motion produces a positive "fluid color" sign as opposed to pleural thickening which provides little or no "fluid color" sign. Careful US examination for additional abnormalities seen on US such as pleural or diaphragmatic nodularity or a parenchymal lesion in adjacent atelectatic or consolidated lung may suggest a malignant etiology of the effusion. Sonographic assessment of the character and overall size of effusions has also been used to stratify patients with parapneumonic effusions into treatment with percutaneous pleural catheter drainage or medical thoracoscopy and to determine if or when intervention with video assisted thoracoscopy (VATS) is required. Recently, US has also been used in research studies to assess the efficacy of pleurodesis and absence of the "gliding sign" between parietal and visceral pleural surfaces during respiration strongly correlating with successful pleurodesis.

Pleural Effusion Etiology

Pleural effusions may occur in patients and be of a known etiology such as cardiac failure and malignancy, or occur in clinical circumstances that are suggestive of their etiology such as pneumonia and sepsis. They may also be the cause of presentation in patients without a known diagnosis such as pulmonary embolic disease or previously undiagnosed malignancy. The radiographic features are in part dependent upon their etiology and are here described according to etiology.

Parapneumonic Pleural Effusion and Empyema

Bacteria are by far the most common cause of pleural sepsis, with up to 40% of patients with pneumonia developing a pleural effusion, although only a minority of these progress to develop a complicated parapneumonic effusion or empyema. Viral parapneumonic effusions are much less common, as are effusions due to fungal infection, with the later usually occurring in association with other disease. Although the diagnosis ultimately relies upon fluid sampling and examination, imaging is an essential tool in management.

Complicated parapneumonic effusion and empyema may first be suspected on CXR in a patient with pneumonia who develops an effusion. No specific radiographic signs distinguish these from other effusions, although loculation, in the

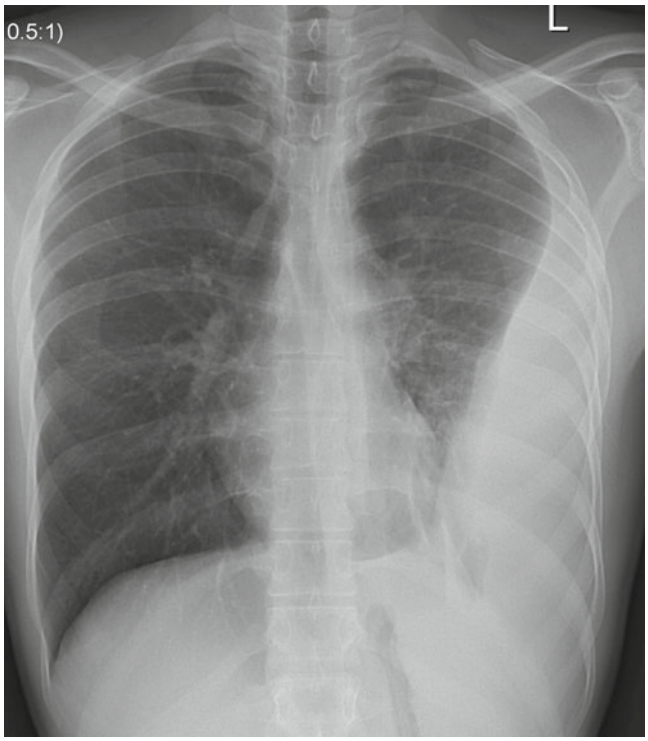

Fig. 54.8 A loculated left-sided complex parapneumonic effusion

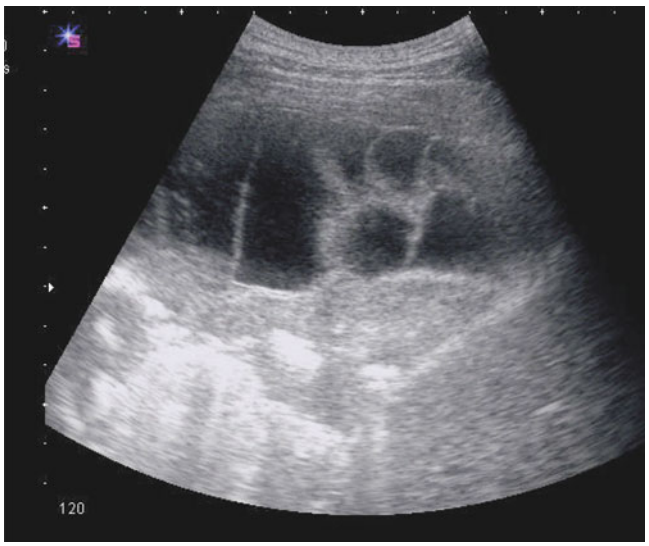

Fig. 54.9 A complex multiseptated pleural collection on US

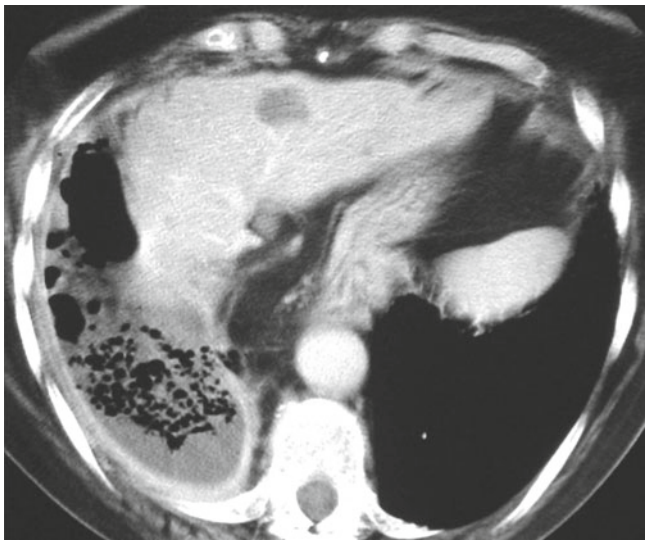

Fig. 54.10 A right-sided empyema, demonstrating pleural enhancement, and multiple septations inferred by the presence of multiple pockets of gas. There is an increase in thickness and attenuation of the adjacent extrapleural fat and rib crowding

absence of a prior history of thoracic trauma, infection, or surgery, is suggestive of a "fibropurulent" or "organized" collection (Fig. 54.8); nondependent foci of gas within the fluid (from gas-forming organisms or following diagnostic tap or percutaneous catheter insertion) suggest the presence of septations, although these are infrequently seen on CXR and more commonly seen on US and MSCT.

A persistent hydropneumothorax following, incomplete drainage, with a thickened visceral pleura preventing reexpansion of the "trapped" lung may be identified on CXR and may necessitate surgical decortication.

US will confirm the presence of fluid and the signs of a complicated parapneumonic effusion such as echogenic fluid and septations (Fig. 54.9), and may demonstrate echogenic foci representing gas, particularly in multiseptated collections. The extent of the collection may not be appreciated by US, and although differentiation from consolidated lung is mostly straightforward, if the effusion fails to resolve with appropriate therapy, an underlying cause is unlikely to be detected. In these circumstances, MSCT may be of value. MSCT may be useful to demonstrate the full extent of an effusion, the degree of loculation, and potentially to guide pleural catheter insertion if patient anatomy or configuration of the collection makes US-guided intervention technically difficult. Although loculation is readily demonstrated on MSCT, septations are mostly not identified, although their presence may be inferred by nondependent gas collections. Several other CT features have been described in complicated parapneumonic effusions and empyema; the most frequently demonstrated finding is parietal pleural thickening and enhancement, which has a high sensitivity and specificity, compared with transudative effusions, and is present in over 90% of cases (Fig. 54.10). Extrapleural changes may also be seen in the subcostal tissues on MSCT, including increased thickness (>2 mm) and attenuation or stranding of the extrapleural fat and soft

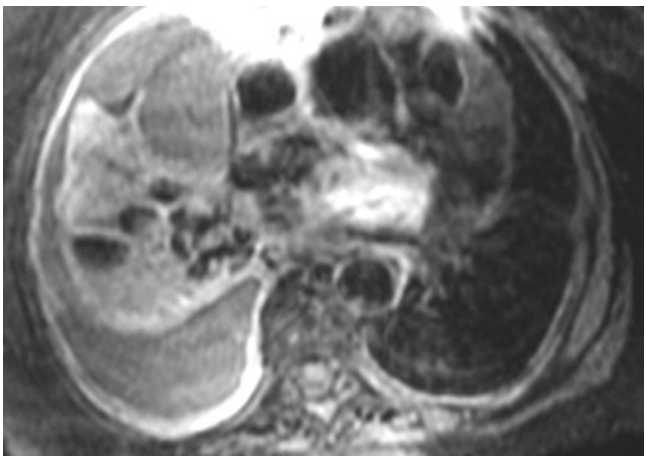

Fig. 54.11 A right-sided empyema, seen on a fat-saturated T1-weighted sequence postgadolinium. It shows the pleural fluid to be of low T1 signal with marked associated pleural enhancement, seen as increased T1 signal

tissue, demonstrated in 70% of patients. Particularly when subtle, the changes may be best appreciated by comparison with the contralateral "normal" side.

Occasionally, a peripheral pulmonary abscess may be difficult to distinguish from a loculated empyema on CXR and may be indistinguishable on US, but several CT features can help to differentiate these two diseases. Abscesses are more commonly spherical and thicker walled and replace rather than displace normal parenchyma and are associated with abrupt vessel cutoff and bronchi at the interface of normal lung. They replace rather than displace lung. Complicated parapneumonic effusions and empyema are more commonly lenticular, thinner walled, and make an obtuse rather than an acute angle with the chest wall, and demonstrate increased attenuation of the extrapleural fat and compression (passive atelectasis) of adjacent lung. The "split pleura" sign of thickened visceral and parietal pleura separated by pleural fluid is relatively sensitive and specific in the differentiation of pleural from pulmonary disease.

There is a relative paucity of literature on MR imaging in complicated parapneumonic effusion and empyema, although many of the CT features have directly correlating MR appearances. The fluid collection has typical appearances, low signal on T1W and high signal on T2W images (Fig. 54.11). The full extent of pleural collections and loculation as with CT are well defined, and in particular, MRI may demonstrate septations not visible on CT. Hemorrhage either spontaneous or secondary to intervention may be identified by heterogeneity in fluid signal intensity.

The use of "Triple Echo" (TE) pulse sequences may allow the differentiation between complex exudates (highest signal), simple exudates (high signal), and transudates (low signal). More recently, diffusion-weighted imaging (DWI) has been shown to separate transudates and exudates, with transudates demonstrating high diffusion and exudates low diffusion, although this is not routinely performed.

Complications of Chronic Pleural Sepsis

Suboptimally treated pyogenic empyema, tuberculosis (TB), and other less common causes of pneumonia such as actinomycosis, aspergillus, and blastomycosis may result in chronic pleural infections, and these may drain spontaneously via the tracheobronchial tree (bronchopleural fistula) or directly through the chest wall (empyema necessitatis). The deposition of a thick inelastic fibrous tissue "peel" over the visceral pleural surface, fibrothorax, may manifest as a late complication of empyema, TB, or hemothorax. This may encase the entire lung with calcification frequently seen on the "inner" surface of this layer on CXR and MSCT. Malignancy has been reported as a late complication of chronic empyema, occurring at least 5 or more years after the initial pleural collection. The tumor types reported include non-Hodgkin lymphoma, squamous cell carcinoma, mesothelioma, malignant fibrous histiocytoma, and sarcoma. New symptoms, particularly of chest wall pain, warrant urgent assessment with MSCT in the first instance.

Bronchopleural Fistula

Most bronchopleural fistulas result from surgical intervention (pneumonectomy) or necrotizing pneumonias; other etiologies include trauma, neoplasia, and radiotherapy. Volumetric MSCT enables three-dimensional reconstructed images to potentially display the entire course of the fistulous communication. Fistulas with ongoing empyema are a difficult clinical problem and may necessitate open drainage, with surgical resection of several ribs and placement of a large-caliber surgical drain vented to the atmosphere (modified Clagett open-window thoracostomy).

Diffuse Benign Pleural Thickening

Diffuse visceral pleural thickening involves the visceral pleura and is most commonly preceded by a pleural effusion with subsequent visceral pleural fibrosis, which then adheres to the parietal pleura. The involvement of the visceral pleura with associated pulmonary parenchymal change enables the diagnosis to be made on both CXR and MSCT. The most common causes of diffuse visceral pleural thickening are prior TB empyema, trauma, drugs, and asbestos exposure.

Asbestos-Related Diffuse Pleural Thickening

The refined International Labor Organization 2003 classification recognizes asbestos-related pleural thickening as diffuse "only in the presence of and in continuity with, an obliterated costophrenic angle." This is commonly associated with pulmonary parenchymal bands and curvilinear areas of atelectasis. Importantly, this localized subpleural parenchymal fibrosis is different from and often present without the diffuse interstitial fibrosis of asbestosis. Bilateral involvement may be confused with prominent extrapleural fat in obese patients but may be distinguished by these usually being symmetrical and not extending to the lateral costophrenic recess, whereas asbestos-related diffuse pleural thickening extends to involve the costophrenic angles, which are blunted, and commonly has associated pulmonary abnormalities.

MSCT is more sensitive than CXR and in determining the extent of diffuse thickening and detecting associated parenchymal changes. MSCT may be used to confirm the presence of diffuse pleural thickening, when there is doubt from the CXR, exclude malignant disease, and detect associated parenchymal disease. On MSCT, diffuse pleural thickening is defined as a continuous sheet of thickening at least 5 cm in lateral extent, 8–10 cm in craniocaudal extent, and 3 mm thickness. The adjacent extrapleural fat is commonly increased in thickness, thought to be secondary to an inflammatory reaction to the pleural retraction. Although MRI is not commonly performed to assess diffuse pleural thickening, it is typically of low signal on T1- and T2-weighted sequences and does not enhance with gadolinium.

Non-asbestos-Related Pleural Thickening

The appearances on CXR and MSCT usually reflect the underlying etiology and often allow a specific etiological diagnosis to be made. The CXR and MSCT features of patients with a prior tuberculous empyema, as described earlier, include unilateral sheetlike calcification often with significant volume loss and associated thickening of the adjacent extrapleural fat. Evidence of associated pulmonary parenchymal and thoracic nodal tuberculous disease may also be evident.

Patients with posttraumatic hemothoraces commonly show pleural thickening associated with multiple healed rib fractures.

Malignant Pleural Thickening

Pleural Metastatic Disease

Metastatic pleural disease is the commonest cause of malignant pleural thickening. It may be present as thickening alone or more commonly associated with a pleural effusion. The commonest underlying primary diseases are bronchogenic carcinoma, 40%; breast carcinoma, 20%; lymphoma, 10%; and gastrointestinal and genitourinary malignancies. Metastatic thymoma also causes malignant pleural thickening by either spreading directly or seeding along the adjacent pleural surface. Massive pleural effusions are most commonly due to malignancy and are usually defined as either complete or near complete opacification of a hemithorax on CXR. The majority of malignant effusions are symptomatic. On CXR, large effusions may be associated with contralateral mediastinal shift. Metastatic unilateral pleural disease may be indistinguishable from malignant pleural mesothelioma. CXR appearances include circumferential thickening, lobulated pleural thickening, pleural effusion (which may be large), rib crowding, and elevation of the hemidiaphragm consistent with volume loss (Fig. 54.12). Large pleural effusions often obscure the underlying associated pleural thickening. Additional features that may be present include pulmonary abnormalities such as nodules and masses, and lymphangitis carcinomatosis, nodal enlargement, and bone metastases. The imaging of malignant effusions is in part dependent upon whether the patient has a known prior or contemporaneous malignancy. Recently, thoracic ultrasound has been shown to be of value in patients with a suspected but unconfirmed malignant pleural effusion and may be used as the first test post-CXR to both guided thoracocentesis and suggests a malignant etiology. Ultrasound was performed in patients with a suspected but not proven malignant effusion and then compared this to contrast-enhanced MSCT and histology. Ultrasound had a sensitivity for the diagnosis of

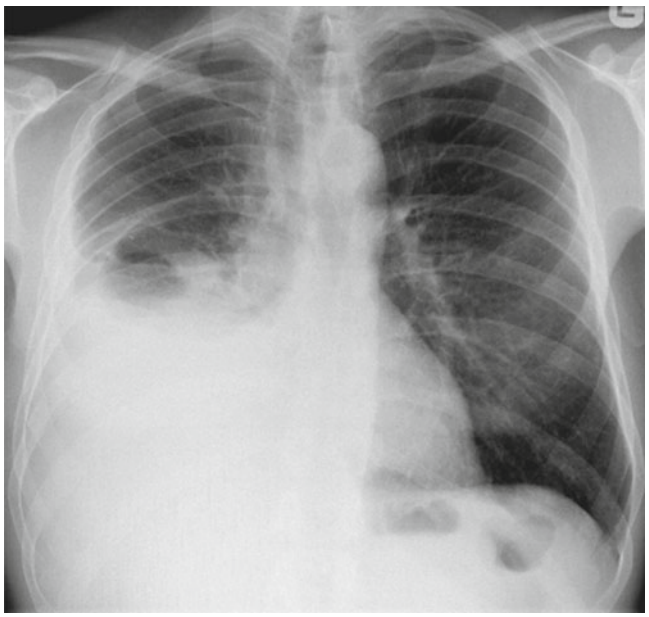

Fig. 54.12 A moderate-sized right-sided effusion, with rib crowding and tracheal and mediastinal deviation to the side of the effusion. These features are suggestive of malignancy

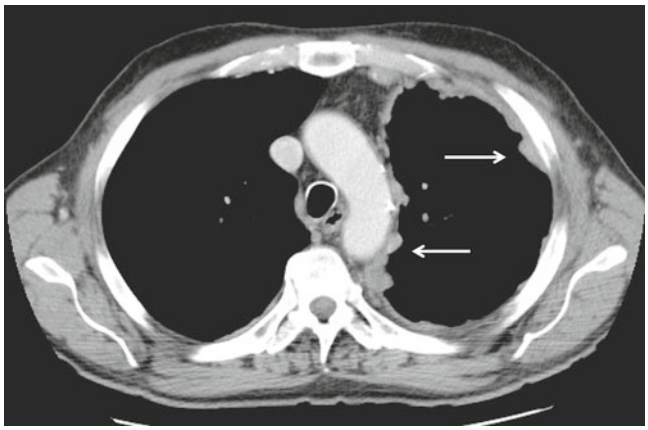

Fig. 54.13 Malignant left-sided pleural thickening (*arrowed*), seen to be nodular, thicker than 1 cm in places, and involving the mediastinal pleural surface

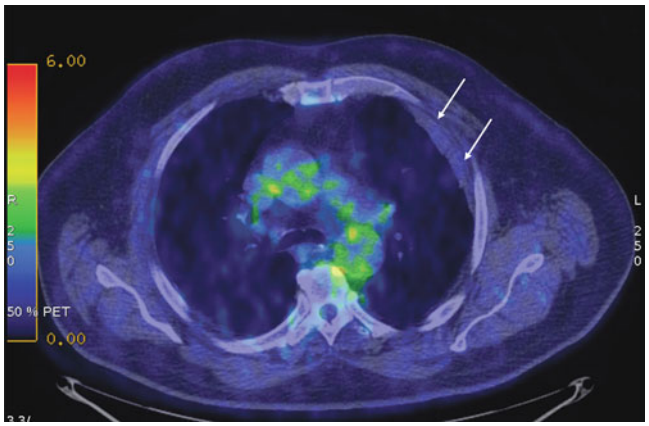

Fig. 54.14 An 18-FDG PET-CT scanning demonstrating an absence of uptake in left-sided pleural thickening (*arrowed*)

malignancy of 73%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 79%.

Contrast-enhanced CT is the imaging modality of choice for demonstrating and differentiating between benign and malignant pleural thickening. It should potentially include the abdomen as this may enable identification of a subdiaphragmatic primary tumor as cause. Features reported to suggest a malignant etiology include parietal pleural thickening greater than 1 cm, circumferential pleural thickening, nodular pleural thickening, and mediastinal pleural thickening (Fig. 54.13). The specificities of these findings have been reported to be between 90% and 100%, although circumferential pleural thickening may be a less reliable indicator of malignant disease in the presence of an effusion. Although MSCT may suggest a diagnosis of malignant disease, histological diagnosis is necessary for a definitive diagnosis.

Magnetic resonance imaging is usually reserved for cases where contrast-enhanced MSCT is contraindicated. MRI allows multiplanar image acquisition and demonstrates excellent soft tissue contrast allowing assessment of extrapleural, chest wall, and diaphragmatic invasion. Although the sequences performed are dependent upon the scanner type, typical sequences include T1W, T2W, and FSTIPG acquisitions. Cardiac and respiratory triggering reduces motion artifact and significantly improves image quality. The differentiation of benign and malignant disease is best performed on T2W and FST1PG sequences. Malignant pleural thickening enhances and demonstrates increased signal intensity compared to intercostal muscle, although this feature is also seen in inflammatory and infective pleural disease. FST1PG sequences have been found to be particularly sensitive at demonstrating focal thickening and enhancement of the interlobar fissures.

Multiple studies have investigated the role of MRI in distinguishing malignant from benign disease using the accepted MSCT criteria for the diagnosis of malignant thickening and suggest that it is as good as MSCT, although these studies did not take into account the ability of MSCT to assess the lung and subdiaphragmatic disease.

PET-CT is now established as an excellent imaging technique in the investigation and management of malignant pleural disease. It has been investigated in distinguishing benign from malignant disease (Fig. 54.14). A recent study suggested that it accurately distinguished benign from malignant asbestos-related pleural disease with a sensitivity of 94.1%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 93.3%. False-positive scans may occur due to infection, benign pleural inflammation, and prior talc pleurodesis, and if this has been performed, PET-CT is of little value (Fig. 54.15). False-negative scans may occur in patients with slow-growing or low-grade malignancy; these tumors exhibit low glycolytic and mitotic activity, accounting for the false-negative results.

Malignant Pleural Mesothelioma

Mesothelioma is the commonest primary pleural tumor. It is nearly always associated with prior asbestos exposure, usually developing after a long latent period of 30–45 years. Fortunately, only 5–7% of individuals exposed to asbestos develop mesothelioma. The majority of patients with mesothelioma present with advanced disease and have a poor prognosis, with a median survival of 12 months. Decreased survival is associated with extensive local disease including intrathoracic lymphadenopathy and distant metastatic disease.

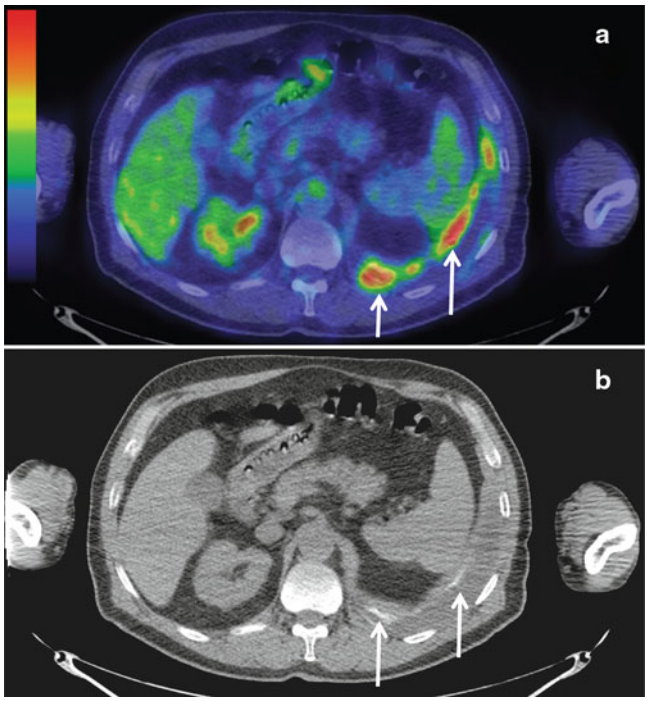

Fig. 54.15 (**a**) A PET-CT scan demonstrating areas of increased FDG avidity at the left costophrenic angle. (**b**) The corresponding CT scan demonstrating talc (*arrowed*) at the sites of the increased avidity

The features on CXR are, as discussed previously, indistinguishable from diffuse metastatic malignant pleural thickening. Unilateral pleural thickening and pleural effusion are the commonest appearances on CXR. Importantly, a large pleural effusion may not result in contralateral mediastinal shift, "fixed mediastinum," due to pleural encasement by tumor. Isolated pleural thickening without an effusion is relatively uncommon, occurring in 10–20% of cases; intrafissural extension is frequent. Occasionally, the CXR appearances are of a progressive decrease in hemithorax size that becomes associated with pleural thickening, known as "hemithorax en cuirasse."

Contrast-enhanced MSCT is the imaging modality of choice for aiding diagnosis, staging, and guiding biopsy in patients with mesothelioma. MSCT enables assessment of the degree of pleural disease and extrapleural extension. Nodular pleural thickening is seen in over 90% of patients, predominantly involving the lower zones with upper zone involvement seen less commonly. Diaphragmatic thickening and fissural involvement and pleural effusions are present in over 80% of patients. MSCT may also demonstrate nodal disease and both pulmonary and distant metastatic disease. The minority of patients with mesothelioma have associated calcified pleural plaques. Chest wall invasion is uncommon but may be seen as loss of the adjacent extrapleural fat plane, intercostal muscle invasion, and adjacent rib destruction, occurring in 15% of patients. MSCT is used to assess disease response in mesothelioma, but the objective measurement of a tumor that arises from the pleura and abuts the chest wall and has irregular margins and associated thoracic distortion is as would be expected problematic. Currently, the gold standard for the assessment of tumor response is measurement on MSCT using the modified Response Evaluation Criteria In Solid Tumors (modified RECIST 1.1). More recent publications suggest that automated or semiautomated measurement may be a more reliable method of measuring tumor response.

MRI, although not routinely necessary, has been shown to be of value in detecting direct tumor extension into the diaphragmatic and endothoracic fascia, enabling differentiation of T3 from T4 disease. Contrast-enhanced MRI (CEMRI) in patients with epithelioid mesothelioma referred for surgery has been shown to detect unexpected unresectable disease that would have precluded surgery.

Although neither MSCT nor MRI is able to distinguish between T1a, T1b, and T2 disease since neither modality can accurately identify the visceral or parietal pleura nor differentiate parietal from visceral involvement, or detect small volume invasion of diaphragmatic muscle or pericardium. The assessment of metastatic nodal involvement is limited using MSCT and MRI in a similar manner to scanning in lung cancer, with sensitivities of 50–60% when nodal size alone is used to predict metastatic disease involvement. There have also been advances in functional imaging using MRI in patients with mesothelioma; with MRI used to assess tumor perfusion and chest wall compliance, both of which may be of value in the future in assessing disease response to antiangiogenic treatment and providing an objective method of comparing clinical symptoms during treatment.

Recent reports have suggested that PET-CT is of value in patients with mesothelioma. It may help differentiate benign from malignant disease and has also been shown to potentially be of use in guiding the site for percutaneous biopsy (Fig. 54.16). It may also potentially have a role in providing prognostic information and in detecting disease response to chemotherapy. Nodal metastatic disease detection appears to be more sensitive than MSCT, and importantly, in addition to improved nodal staging, metastatic disease appears more reliably detected (Fig. 54.17).

PET-CT may detect disease response to chemotherapy earlier than MSCT, by demonstrating a reduction in 18-fluorodeoxyglucose (FDG) metabolism, known as a metabolic response, rather than wait for a reduction in tumor volume known as an anatomic or structural response on MSCT. This may be assessed subjectively by visual assessment of the degree of avidity, or semiquantitatively by combining visual response with measuring the standardized uptake value (SUV), or by using a novel method of quantifying FDG activity, the total glycolytic volume (TGV), which

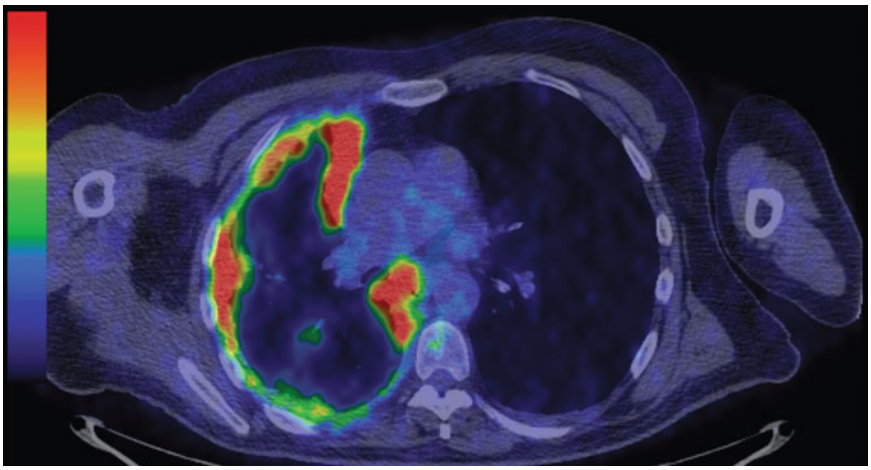

Fig. 54.16 An FDG PET-CT scan demonstrating heterogeneous avidity and suggesting that a posterior percutaneous biopsy may be nonrepresentative and potentially nondiagnostic

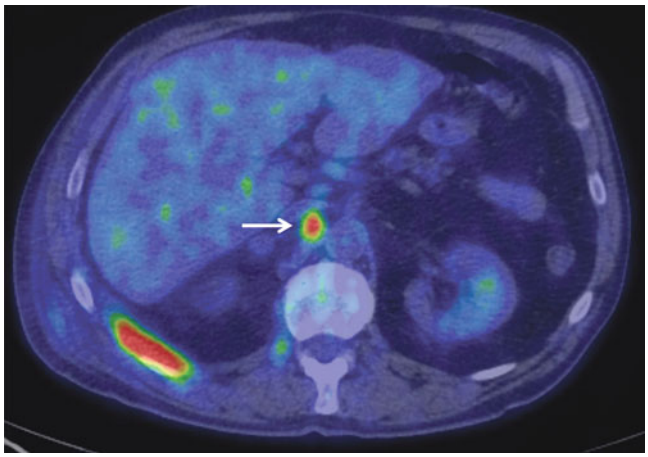

Fig. 54.17 An FDG PET-CT scan with avidity at the right costophrenic angle and an FDG avid metastatic subdiaphragmatic retrocaval lymph node (*arrowed*)

takes into account the volumetric activity of FDG in the whole hemithorax. Semiquantitative measures of an early metabolic response have been shown to correlate with a median time to tumor progression, and measurement of TGV appears to predict response to chemotherapy and patient survival after 1 cycle of chemotherapy.

Focal Pleural Thickening

Pleural Plaques

Pleural plaques are the most common pleural lesions encountered in everyday radiological practice after pleural effusions. They are almost exclusively seen in asbestos-exposed patients, and their prevalence in this patient population is dependent upon the exposure dose and the elapsed time since exposure. They are almost exclusively seen on the parietal pleural surface, although there are case reports of plaques involving the interlobar fissures. They are most evident radiographically when calcified. On MSCT, they appear as flat pleurally based lesions with nontapered edges. They typically involve the costal and paravertebral surfaces.

Solitary Fibrous Tumors or Pleural Fibromas

These are uncommon tumors accounting for less than 5% of all pleural tumors. They are mostly benign and slow growing, with malignant/sarcomatous degeneration seen rarely, and predominantly in larger tumors. They arise from the visceral surface and may be pedunculated. On CXR, they commonly appear as smooth rounded opacities abutting the pleura. On MSCT, their appearance is partly size dependent, with smaller tumors demonstrating homogeneous enhancement and their relationship to the pleura readily appreciated. Larger tumors may have areas of calcification within them and demonstrate a characteristic heterogeneous enhancement pattern (Fig. 54.18).

Lipomas and Liposarcomas

Lipomas are benign asymptomatic rare pleural tumors, most commonly diagnosed as an incidental finding on CXR and CT. The pleural origin and fat density of these tumors is commonly not appreciated on CXR but is readily confirmed by MSCT. On MSCT, lipomas are of uniform, low fat attenuation. In some tumors, linear and curvilinear soft tissue stranding may be present. MRI appearances are of a well-defined homogeneous mass, hyperintense on T1W, and moderately intense on T2W images. Fat suppression sequences may be of value. Liposarcomas are also rare and typically are larger than benign lipomas on presentation. They commonly infiltrate the adjacent intercostal muscles

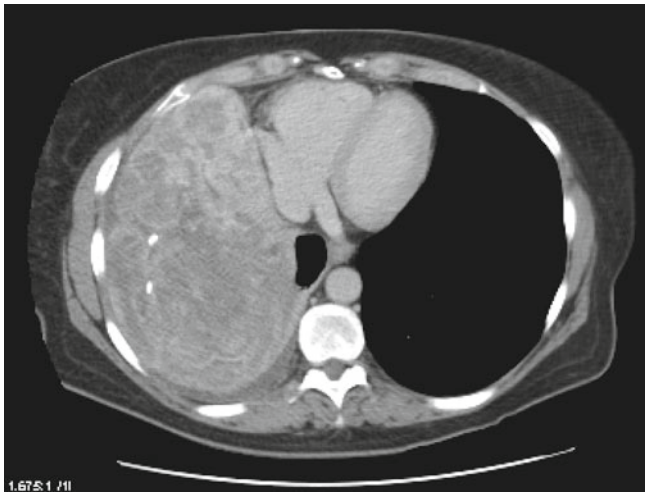

Fig. 54.18 A large right-sided heterogeneously enhancing benign pleural fibroma, containing flecks of calcification within it

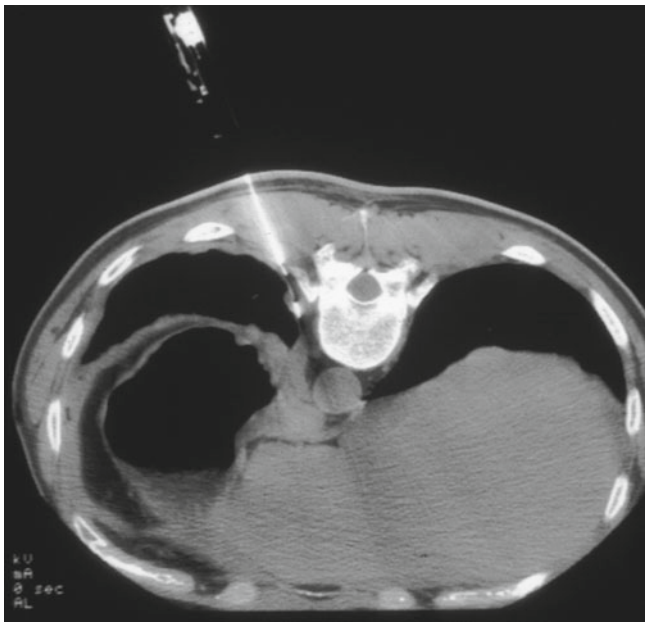

Fig. 54.19 A CT-guided cutting needle biopsy of nodular irregular malignant pleural thickening

and tissues and may be symptomatic, presenting with pain or soft tissue swelling. They do not appear to arise from preexisting lipomas. They are seen as heterogeneous masses on MSCT with soft tissue and fat components and with HUs of less than 50 pre- and post-intravenous contrast enhancement. On MR, they return high signal on T2W sequences due to myxoid degeneration and low signal on T1W sequences.

Pleural Intervention

The advantages of image guidance for thoracocentesis and chest drain insertion are well established and discussed elsewhere. Image-guided pleural biopsy has also been shown to be of benefit when compared to nonguided procedures. Approximately 40% of malignant effusions are not confirmed by effusion aspirate alone and require additional imaging and biopsy. These patients plus those with unexplained pleural thickening with or without an associated effusion require histological biopsy to achieve a diagnosis. In the majority of these patients, this may be by either medical thoracoscopy or image-guided biopsy. Only in areas endemic for TB is non-image-guided pleural biopsy routinely performed.

The yield for malignancy is approximately 50% for non-image-guided compared to 90% for image-guided pleural biopsy in patients with pleural effusions, and up to 100% in patients with pleural thickening alone biopsied under MSCT guidance (Fig. 54.19). The use of either US or MSCT is determined by individual preference, expertise, availability, and cost. Both techniques probably have the same diagnostic yield and rate of complications in patients with pleural thickening and effusions, although MSCT is superior in patients with thickening alone. Complication rates are low for either technique when performed by an experienced operator, ranging from 0% to 10%. Contraindication to biopsy is similar to nonguided procedures, including hemorrhagic diathesis, uncontrollable dyspnea, and coughing.

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Pleural Manometry

55

David Feller-Kopman

Introduction

It is not known why human evolved to have a pleural space. Elephants, for example, do not have a pleural space and do not have any adverse effects. It is thought that their lack of a pleural space prevents parenchymal injury during "snorkeling." Similarly, patients who have had pleurodesis generally do not suffer adverse respiratory problems from their lack of a pleural space. Nonetheless, the presence of air or fluid in the pleural space will change intrapleural pressure (Ppl) and can affect the lung, chest wall, and cardiovascular system. The German internist Heinrich Quincke, in 1878, is credited as performing the first measurements of pleural pressure (Ppl). The clinical use of pleural manometry became popular in the early twentieth century when inducing pneumothorax for the treatment of tuberculosis was the standard of care. It was also noted at that time that approximately 5% of patients would develop "unexpandable lung" due to parenchymal or visceral pleural scarring, with the formation of a pleural effusion ex vacuo. The importance of negative pleural pressure was also appreciated during the influenza epidemic of 1917–1918 (see chapter on empyema). The monitoring of pleural pressure, though interesting from a physiological standpoint in and of itself, is now often used clinically to minimize the pressure-related complications associated with thoracentesis including the development of symptoms, such as chest discomfort and reexpansion pulmonary edema, as well as to predict the success of pleurodesis in patients with malignant effusions. Though the last three decades have seen a resurgence of using pleural manometry in the care of patients, it remains an underutilized technique. This chapter will review the pressure physiology of the pleural space and discuss the clinical application of manometry.

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Normal Pleural Pressure Physiology

Normal pleural pressure at functional residual capacity (FRC) is slightly subatmospheric, approximately −3 to −5 cmH_20. This results from the balance of forces produced by the elastic recoil forces of the lung and the tendency of the chest wall to expand. One should note that pleural pressure actually consists of pleural liquid pressure and pleural surface pressure. The difference between these two pressures relates to deformation forces created by areas of parietal and visceral pleural contact. These deformation forces result in a pleural liquid pressure that is slightly more subatmospheric than one would expect based solely on the recoil pressures of the lung and chest wall.

There are two dominant theories regarding pleural pressure physiology. One school of thought is based upon the "hydrostatic theory" that pleural liquid is in a hydrostatic equilibrium maintained by a vertical gradient in pleural pressure of 1 cmH_20/cm height. When fluid accumulates in the pleural space, the deformation forces are in part released, and three distinct pressure zones are created. In the upper zone, the thickness of the pleural liquid is normal, and the pleural liquid pressure remains lower than the pleural surface pressure. In the middle zone, where pleural liquid thickness starts to increase, to where pleural liquid pressure becomes zero, pleural liquid pressure is equal to pleural surface pressure. In the lower zone, the pressure of pleural liquid is positive, and the lung and chest wall are pushed apart.

Another model maintains that pleural liquid pressure is always equal to pleural surface pressure. This concept suggests that pressure gradients due to gravity and regional differences in pleural surface pressure drive a small viscous flow of fluid in the pleural space and requires the presence of a small continuous pleural fluid space with no contact between the lung and chest wall. As pleural fluid accumulates, the viscous resistance to flow falls rapidly, and the gradient in the pleural pressure approaches that of the hydrostatic pressure gradient of 1 cmH_20/centimeter of height.

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Measurement of pleural liquid and surface pressure in a normal pleural space is technically challenging due to the fact that the normal pleural space is only approximately 20 μm thick and the insertion of any device into the pleural space will create deformation forces not present prior to the insertion of the device. Though there continues to be debate between the two dominant theories of normal pleural pressure physiology, these conceptual differences may only be of practical importance at the termination of a thoracentesis, when there is only a physiologic amount (5–8 mL) of pleural fluid present. In the presence of even a clinically small effusion (several hundred milliliters), one can measure Ppl with a variety of techniques as the viscous resistance to flow becomes negligible. The pressure measured, therefore, is an accurate representation of the hydrostatic pressure in the effusion at the level of the catheter/transducer insertion site.

It has been suggested that the location of the catheter (or other device) relative to the height of the pleural effusion is insignificant. The argument holds that as Pascal's law states, in an enclosed system such as the chest, pressure is transmitted equally in all directions and will exert the same force on the lung, chest wall, and manometer, regardless of where the needle is inserted. More realistically, however, a hydrostatic pressure gradient of 1 cmH_20/cm height *is present*, and so the pressure read by the manometer represents the pressure at a specific level and not the pressure throughout the hydrothorax. With the removal of pleural fluid and a reduction in the height of the fluid column above the catheter, the influence of the hydrostatic pressure gradient becomes less. The measured Ppl therefore *does* depend on where in the effusion the catheter is placed. Placing the catheter at the most dependent part of the effusion has the *potential* benefits of (1) maximizing the amount of fluid that is able to be removed and (2) minimizing the creation of deformation forces from the contact of the catheter with the lung. With this approach, the pressure measured at the level of the catheter will reflect the pressure in the pleural space and hence the pressure exerted on the lung and chest wall at that level. The disadvantage of placing the catheter dependent is the pressures measured earlier in the procedure are subject to a greater hydrostatic column than later measurements. Placing the catheter more superiorly will minimize the effect of this hydrostatic column, but may increase the risk of pneumothorax due to less distance between the visceral and parietal pleurae. Pascal's law does, however, tell us that the *change* in pressure as fluid is removed will be the same, regardless of the insertion site of the catheter.

As fluid accumulates in the pleural space, the Ppl will be dependent on the cause of the effusion. In cases of increased pleural fluid production or decreased pleural fluid clearance, pleural pressure increases, causing expansion of the chest wall as well as compression of the lung. As fluid is removed, one expects the lung to expand, the chest wall contract, and the Ppl reach its steady state at FRC. Pleural pressure, however, can be negative, as in the case of trapped lung, or start out positive and drop rapidly as is the case with lung entrapment.

Definitions: Lung Entrapment Versus Trapped Lung

In 1980, Light and colleagues used a U-shaped water-filled manometer connected to an Abram's needle to measure mean pleural pressure during thoracenteses in 52 patients with the goals of determining the clinical utility of pleural manometry and to evaluate the safety of large-volume thoracentesis. Pleural fluid was removed until the mean Ppl fell $< -20\ cmH_20$, no more fluid could be obtained, or patients developed symptoms described as more than minimal in severity. Though the initial Ppl varied widely ($-21\ cmH_20$ to $+8\ cmH_20$), an initial pressure of $< -5\ cmH_20$ was seen only in patients with malignant effusions or "trapped lung." They also measured pleural elastance (change in pressure divided by change in volume) and described three distinct pleural elastance curves: (1) removal of a large amount of fluid with minimal change in pressure (normal pleural elastance, as can be seen in patients with hepatic hydrothorax or congestive heart failure), (2) a relatively normal initial curve followed by a sharp drop in pressure ("lung entrapment"), and (3) a negative initial pressure with a rapid drop in pressure ("trapped lung") (Fig. 55.1).

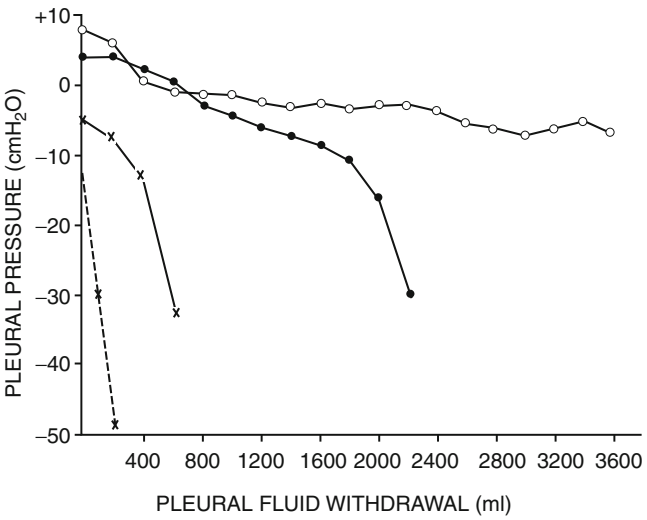

Fig. 55.1 Pleural elastance curves. *Open circle* = normal elastance, *closed circle* = lung entrapment, x = trapped lung (Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Light RW, Jenkinson SG, Minh VD, George RB. Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis. Am Rev Respir Dis. 1980;121:799–804, Official Journal of the American Thoracic Society, Diane Gern, publisher)

A pleural elastance >25 cmH_20/L was seen in patients with malignancy or trapped lung.

Though confusing terms, "lung entrapment" and "trapped lung" describe different pathophysiology. Lung entrapment describes an inability of the lung to fully reexpand during thoracentesis and can be due to visceral pleural thickening, parenchymal disease, or airway obstruction. Parenchymal diseases such as interstitial lung disease and lymphangitic carcinomatosis lead to an increase in the elastic recoil of the lung and may inhibit full lung reexpansion. Likewise, endobronchial obstruction can cause atelectasis and a drop in Ppl. Patients often present with dyspnea related to the effusion as well as with signs and symptoms related to the underlying disease. Chest discomfort or other signs of pleural inflammation may also be present. The effusion associated with lung entrapment is typically exudative, due to active pleural inflammation. The initial Ppl is usually positive and drops steeply toward the terminal portion of the thoracentesis, as a result of the lung not fully expanding. With normal healing of the underlying process, the effusion may completely resolve without any resultant thickening of the visceral pleura.

Trapped lung, on the other hand, represents the sequelae of prior pleural inflammation resulting in visceral pleural thickening. This creates negative pressure in the pleural space and results in an "effusion ex vacuo" – the negative Ppl is the *cause* of the effusion. Since there is no active pleural inflammation, patients typically present with a chronic, and asymptomatic, effusion that is identified on routine physical exam or chest X-ray. As the effusion is due to an excess of negative pleural pressure, it is rare to see contralateral mediastinal shift on a chest radiograph, even in the presence of a moderate–large effusion. Likewise, as the effusion is due to an imbalance of hydrostatic forces, it is almost always transudative in nature. Since the large majority of these patients are asymptomatic, therapy aimed at the pleural effusion is usually not required. The rare patient with trapped lung who is dyspneic from the effusion typically has a restrictive ventilatory defect, and decortication may be required to expand the underlying lung.

Lung entrapment and trapped lung are part of a continuum of the natural healing process of the underlying disease. As such, one may occasionally obtain pleural fluid results that fall in the exudative range in the setting of trapped lung physiology, depending on when the thoracentesis is performed in the healing process. Likewise, if a patient has multiple problems, such as pneumonia with high pleural elastance and congestive heart failure, transudative fluid may be obtained with lung entrapment physiology. Additionally, especially in the setting of lung entrapment, one should evaluate the different phases of pleural elastance. Though *overall/mean* elastance can be low, especially if the majority of fluid is removed in the setting of a normal elastance, the terminal part of the curve will have high elastance, and this can be overlooked if pressures are not measured frequently enough. We typically measure a Ppl once a fluid column is obtained (opening pressure) and every 240 cc. If pressures are falling (i.e., the slope of the elastance curve is changing) or the patient develops chest discomfort, we measure pressure more frequently. It is therefore crucial to interpret Ppl and elastance within the specific clinical context.

PPL and Pneumothorax

Though the mechanisms of pneumothorax in the setting of nonexpandable lung are not fully understood, it is likely that with a reduction in Ppl, atmospheric air either enters the pleural space around the catheter/via the catheter tract or the drop in Ppl causes local deformation forces that cause a small tear in the visceral pleura. The use of vacuum bottles to drain fluid has been associated with a higher incidence of pneumothorax. Unlike using a syringe pump system and intermittently measuring Ppl, it is likely that the vacuum bottles continue to drain fluid even when the lung is not able to expand, creating a vacuum in the pleural space itself.

Techniques of Measuring Pleural Pressure

Pleural pressure can be measured via in several ways, including using a U-shaped water manometer, an "overdamped" water manometer, or sophisticated electronic transducer systems. A benefit of the U-shaped manometer is the fact that it is relatively inexpensive. A disadvantage, however, is the fact that it may be difficult to accurately record values due to the inspiratory and expiratory pleural pressure swings. Doelken et al. have recently described their use of an overdamped water manometer that uses a 22-ga needle as a resistor and have shown excellent correlation to the electronic system ($r=0.97$). The benefits of this system are that it is relatively easy to set up, and that it also provides real-time mean Ppl without the large respirophasic swings that are encountered with systems that are not damped. Electronic transducer systems can be configured to standard intensive care unit (ICU) monitors; however, as these monitors are not calibrated to measure negative pressure, one needs to calibrate an "offset." Additionally, ICU hemodynamic transducers report data in mmHg, as compared to the standard cmH_20 typically used for Ppl measurements. This problem is easily resolved by using the conversion factor of 1 mmHg = 1.36 cmH_20. A clear advantage of using an electronic transducer system is the ability to review the Ppl curves after the data has been collected and analyze pressure anywhere in the respiratory cycle (i.e., end-inspiratory, end-expiratory, as well as mean Ppl). Most authors currently

report mean or end-expiratory (i.e., FRC) Ppl. It may be, however, that end-inspiratory pressure is most related to the development of pressure-related complications such as chest discomfort and reexpansion pulmonary edema.

PPL and Symptoms

Careful attention should always be paid to patient symptoms during the removal of pleural fluid, especially when formal pressure measurements are not being obtained. Whereas sharp pain, typically felt over the ipsilateral shoulder, may be due to diaphragmatic irritation by the catheter, a more vague chest discomfort has been shown to correlate with potentially dangerous drops in Ppl. Interestingly, in this study, there was a trend toward a lower pleural elastance in the patients who developed cough, possibly suggesting that cough is due to normal expansion of the lung/resolution of atelectasis as the pleural fluid is removed, and one need not terminate a thoracentesis solely for the development of cough. It should also be noted that nearly 9% of patients in this study had Ppl < -20 cmH_20 without any symptoms, and it is therefore not uncommon to see patients who have a basilar pneumothorax with visceral pleural thickening after a large-volume thoracentesis who have nonexpandable lung and normal pleural elastance.

Other Clinical Uses of Manometry

Light's group also investigated the relationship between changes in Ppl during thoracentesis and improvement in lung function. While improvement in FVC following thoracentesis was related to the volume of fluid removed (approximately 21 mL for each 100 mL removed), the correlation coefficient was only 0.49. Improvement in FVC was also significantly (and negatively) related to initial Ppl, as well as the change in Ppl. The negative correlation indicates that the larger pressure changes were associated with smaller improvements in FVC, consistent with the physiology of nonexpandable lung.

Huggins and colleagues have recently described their use of an "air contrast" CT scan to visualize visceral pleural thickness and help define the cause of unexpandable lung in a group of 247 consecutive patients undergoing pleural manometry during thoracentesis. They identified 11 patients with a clinical diagnosis of trapped lung. All of these patients developed a mean Ppl < -25 cmH_20 and had prior pleural fluid analysis that was not suggestive of malignancy or pleural inflammation. At the termination of the therapeutic thoracentesis, they instilled atmospheric air, intentionally creating a "diagnostic pneumothorax" with the goal of raising the Ppl to a more physiologic mean of -5 cmH_20 and decreasing the chest discomfort associated with lower Ppl. A subsequent CT scan confirmed visceral pleural thickening in all 11 patients. As expected, all of these patients had a high pleural elastance (Eps > 19 cmH_20/L). The authors favor using the air contrast CT as part of the diagnostic approach to patients with trapped lung as a way to minimize additional pleural interventions, such as attempts at pleurodesis, that will have a low likelihood of success.

In 1980, Light stated that, "as the operator cannot easily estimate pleural pressure…therapeutic thoracentesis should be limited to 1,000 mL unless pleural pressures are monitored." A pressure of -20 cmH_20 was arbitrarily chosen based on prior animal studies that showed a minimal risk of reexpansion pulmonary edema (RPE) if Ppl was kept above -20 mmHg (approximately -27 cmH_20), but a significant risk was present with Ppl of -40 mmHg (approximately -54 cmH_20). Of note, this was a study of pneumothorax, not effusion, in an animal model, and the physiology of RPE may be different in humans with pleural effusions. The above quote has led to the majority of clinicians terminating thoracentesis after removing 1,000–1,500 mL without regard to the amount of remaining pleural fluid, the potential benefit of removing that fluid or consideration of pleural pressure. Light's pneumothorax study suggests that the development of RPE *may* be related to Ppl. Several subsequent studies have shown that large volumes of pleural fluid can be safely withdrawn as long as pleural pressures are monitored, and that RPE is likely an idiosyncratic phenomenon, not necessarily related to Ppl or volume of fluid removed. The benefits of large volume thoracentesis include maximizing symptomatic relief, aiding future diagnostic studies such as chest CT scans, sparing additional procedures (i.e., a therapeutic thoracentesis after an initial diagnostic thoracentesis), as well as demonstrating nonexpandable lung.

Draining the pleural space dry may be especially important when selecting patient for pleurodesis. For pleurodesis to be successful, the pleural surfaces need to appose each other. If the lung is entrapped and does not reexpand during thoracentesis, the odds of successful pleurodesis are reduced. This fact is likely the single largest confounder in the multiple studies comparing pleurodesis agents, as documentation of lung reexpansion was used as a criterion prior to randomization in only two studies. Lan and colleagues found that a pleural space elastance of ≥ 19 cmH_20 after the removal of 500 mL of pleural fluid was associated with pleurodesis failure. Pleurodesis should not be attempted prior to documentation of full lung expansion.

It has been suggested that the reduction in dyspnea following thoracentesis is due to a reduction in the size of the thoracic cage, allowing the inspiratory muscles to operate at a more efficient part of their length–tension curve. This is critical to understand because it is possible to achieve a reduction in dyspnea, that is, pleural palliation, even if the

lung does not fully reexpand after thoracentesis. For patients with malignant effusions who have an improvement in dyspnea and have an expandable lung, options for pleural palliation include pleurodesis or insertion of a tunneled pleural catheter (TPC). If the patient's dyspnea improves but the lung does not expand, the TPC should be the treatment of choice for the majority of patients.

Conclusion

In conclusion, pleural manometry provides an understanding of the underlying pleural pathophysiology and aids the physician in both diagnostic and therapeutic decisions. Measurement of Ppl can distinguish between lung entrapment and trapped lung, allows for the safe removal of large effusions, and is a useful tool to select appropriate patients with malignant pleural effusions for pleurodesis. If formal manometry is not performed during thoracentesis, the symptom of a vague chest discomfort can be used as a surrogate for potentially dangerous drops in pleural pressure.

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Thoracentesis

56

Sara R. Greenhill

Introduction

Pleural effusions can cause significant symptoms of cough, fatigue, pleuritic chest pain, increasing dyspnea, and respiratory distress. Physical examination and chest radiograph can confirm the suspected diagnosis. It is caused by a disturbance between the normal pleural fluid formation and removal. It may not be solely a disease of the chest, but may be a manifestation of many diseases throughout the body, such as organ dysfunction of the cardiac, renal, or liver systems, or other systemic inflammatory diseases, such as rheumatoid arthritis or systemic lupus erythematosus. A thorough history and physical examination, laboratory testing, and possible chest imaging should be completed prior to thoracentesis or sampling of the pleural fluid.

Symptoms of pleural effusion depend on the rapidity of fluid accumulation. Patients with shorter-term fluid buildup will likely be more symptomatic than those in which the fluid accrues over multiple weeks or longer. Symptoms may also depend on the underlying disease. Patients with nephrotic disease, for example, will typically be less symptomatic than those with congestive heart failure or a parapneumonic effusion from bacterial pneumonia. Whether the cause is clear or not and whether the patient is symptomatic or not, a new pleural effusion should be evaluated by thoracentesis to confirm the diagnosis and ensure an unsuspected diagnosis is not the underlying causative factor.

With the presence of pleural fluid, there is an increased distance between the lung and chest wall, interfering with sound transmission through the stethoscope. Changes in auscultation depend on the amount of fluid accumulation. It is difficult to detect fluid less than 250–300 cm^3. Auscultation of pleural fluid becomes possible at volumes of about 500 cm^3, with dullness to percussion and decreased fremitus. When volumes of pleural fluid approach 1,000 cm^3, there is decreased expansion of the ipsilateral chest wall and absence of inspiratory retraction. With greater than 1,000 cm^3 and more lung compression, the physician can see bulging of the intercostal spaces and absence of breath sounds over the majority of the chest with bronchovesicular breath sounds at the apex (Table 56.1).

Chest radiograph can aid in the differential diagnosis. If the effusion is bilateral, it is typically transudative (see below) and due to congestive heart failure, renal failure, or hypoalbuminemia. Cardiac enlargement is frequently seen in congestive heart failure. If a bilateral effusion is found to be exudative (see below), malignancy is most common, but can be seen with lupus pleuritis and rheumatoid pleurisy as well. When an isolated pleural effusion is the only abnormality, the physician should suspect infectious causes such as bacterial or tuberculous infections, in the right clinical setting. Rheumatoid pleurisy and lupus pleuritis can also present with an isolated effusion. Interstitial infiltrates in the setting of a pleural effusion are consistent with volume overload and congestive heart failure, rheumatoid disease, asbestos pulmonary disease, lymphangitic carcinomatosis, sarcoidosis, and lymphangioleiomyomatosis (LAM), among others. Nodular disease suggests malignancy but may also be seen with sarcoidosis and rheumatoid disease (Table 56.2).

Pleural Fluid Analysis: Briefly

Pleural fluid can establish a definitive diagnosis in a limited number of diseases, such as empyema, malignancy, chylothorax, and rheumatoid pleurisy. However, it is highly useful in excluding potentially harmful diseases that would warrant immediate intervention, such as empyema.

Initial evaluation of the fluid is performed at the time of thoracentesis, as the fluid is aspirated. Careful attention should be paid to the color (straw colored, serosanguinous,

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Table 56.1 Volume of pleural fluid and associated findings on physical examination

Volume of pleural fluid	Physical examination findings
<250–300 cm^3	Probable normal examination
500 cm^3	1. Dullness to percussion
	2. Decreased fremitus
	3. Normal vesicular breath sounds but decreased intensity
1,000 cm^3	1. Absence of inspiratory retraction, mild bulging of intercostal spaces
	2. Decreased expansion of ipsilateral chest wall
	3. Dullness to percussion up to the scapula and axilla
	4. Decreased or absent fremitus posteriorly and laterally
	5. Bronchovesicular breath sounds
	6. Egophany (E to A change) at the upper level of the effusion
Massive (filling the hemithorax)	1. Bulging of intercostal spaces
	2. Minimal to no ipsilateral chest wall expansion
	3. Dull or flat percussion
	4. Absent breath sounds
	5. Egophany at the apex
	6. Palpable liver or spleen due to diaphragmatic depression

Table 56.2 Chest radiograph findings of specific diseases

Chest radiograph findings	Diseases
Unilateral effusion	Infection
	Lupus pleuritis
	Rheumatoid pleurisy
	Metastatic malignancy, non-Hodgkin lymphoma, leukemia
	Pulmonary embolism
	Drug-induced pleural disease
	Yellow nail syndrome
	Hypothyroidism
	Uremic pleuritis
	Chylothorax
	Constrictive pericarditis
With mediastinal shift	Metastatic malignancy
Without mediastinal shift	Lung cancer
	Malignant mesothelioma
Diseases below the diaphragm	Transudative: hepatic hydrothorax, nephritic syndrome, urinothorax, peritoneal dialysis
	Exudative: pancreatitis, Meigs syndrome, chylous ascites, subphrenic/hepatic/splenic abscess
Bilateral effusion	Transudative: congestive heart failure, nephrotic syndrome, hypoalbuminemia, peritoneal dialysis, constrictive pericarditis
	Exudative: malignancy, lupus pleuritis, rheumatoid pleurisy
Associated with interstitial infiltrates	Congestive heart failure
	Rheumatoid disease
	Asbestos pulmonary disease
	Lymphangioleiomyomatosis (LAM)
	Viral and mycoplasma pneumonia
	Sarcoidosis
	Pneumocystis jiroveci pneumonia
Associated with multiple nodules	Cancer
	Wegener granulomatosis
	Rheumatoid disease
	Septic pulmonary embolism
	Sarcoidosis
	Tularemia

bloody, white), consistency (pus, turbid, debris), and odor (foul smelling) of the fluid.

After visual inspection during the procedure, the fluid is sent for laboratory analysis. Broad classification of the fluid into transudative or exudative by chemical analysis is performed (Tables 56.3 and 56.4). Richard Light established a well-known algorithm for distinguishing an exudative pleural effusion based on three tests: (a) pleural fluid lactate dehydrogenase (LDH) >two-thirds the laboratory's upper limit of normal for serum, (b) pleural fluid to serum LDH ratio >0.6, and (c) pleural fluid to serum protein ratio >0.5. Only one of these results needs to be positive to confirm an exudative effusion. Light's criteria has a diagnostic accuracy over 90 % but drops significantly to below 70–80 % if one of the three categories is borderline. Pleural fluid can also be analyzed for a number of other laboratory tests, including but not exclusive, to glucose, pH, amylase, cholesterol, albumin, B-type natriuretic peptide (BNP), and adenosine deaminase (ADA). There are many other tests and ways to analyze the pleural fluid from a thoracentesis, but that is outside the scope of this chapter.

Indications and Contraindications

The major indication for thoracentesis is the evaluation of the initial presentation of a pleural effusion, unless volume overload is obvious, such as typical congestive heart failure (CHF).

Thoracentesis is contraindicated in patients with bleeding disorders until the abnormality has been corrected, unless emergent. However, even in the setting of anticoagulation administration or thrombolytics, using a small-bore needle can be done safely without increased risk of bleeding. This holds true as well in patients with renal disease and elevated creatinine and uremia levels causing platelet dysfunction. Use of pleural ultrasound at the time of the procedure also

Table 56.3 Causes of exudative pleural effusions

Causes		
Infectious	**Malignancy**	**Connective tissue disease**
Bacterial pneumonia	Carcinoma	Lupus pleuritis
Tuberculous effusion	Lymphoma	Rheumatoid pleurisy
Fungal disease	Mesothelioma	Mixed connective tissue disease
Atypical pneumonias	Leukemia	Sjögren syndrome
Nocardia, *Actinomyces*	Chylothorax	
Subphrenic abscess		
Hepatic abscess	**Other inflammatory**	**Endocrine dysfunction**
Splenic abscess	Pancreatitis	Hypothyroidism
Hepatitis	BAPE	Ovarian hyperstimulation syndrome
Spontaneous esophageal rupture	Pulmonary infarction	
Parasites	**Radiation therapy**	**Lymphatic abnormalities**
	Sarcoidosis	Malignancy
Iatrogenic	PCIS	Chylothorax
Drug-induced	Hemothorax	Yellow nail syndrome
Esophageal perforation	ARDS	Lymphangiomyomatosis (chylothorax)
Esophageal sclerotherapy	Cholesterol effusion	Lymphangiectasis
Central venous catheter misplacement/ migration		
Enteral feeding tube in pleural space		
	Increased negative intrapleural pressure	**Movement of fluid from abdomen to pleural space**
	Atelectasis	Acute pancreatitis
Vasculitis	Trapped lung	Pancreatic pseudocyst
Wegener granulomatosis		Meigs syndrome
Churg–Strauss syndrome		Carcinoma
Familial Mediterranean fever		Chylous ascites

ARDS acute respiratory distress syndrome, *BAPE* benign asbestos pleural effusion, *PCIS* post-cardiac injury syndrome

Table 56.4 Causes of transudative pleural effusions

Diagnosis	Comment
Congestive heart failure	Acute diuresis can increase pleural fluid protein and LDH concentrations
Cirrhosis	Uncommon without clinical ascites
Nephrotic syndrome	Typically small and bilateral; unilateral, larger effusion may be due to pulmonary embolism
Peritoneal dialysis	Large right effusion may develop within 48 h of initiating dialysis
Hypoalbuminemia	Edema fluid rarely isolated to pleural space; small bilateral effusions
Urinothorax	Unilateral effusion caused by ipsilateral obstructive uropathy
Atelectasis	Small effusion caused by increased intrapleural negative pressure; common in ICU patients
Constrictive pericarditis	Bilateral effusions with normal heart size
Trapped lung	Unilateral effusion from imbalance in hydrostatic pressures from a remote inflammatory process
Superior vena caval obstruction	Due to acute systemic venous hypertension or acute obstruction of lymphatics
Duropleural fistula	Cerebrospinal fluid in pleural space; β2-transferrin diagnostic

ICU intensive care unit, *LDH* lactate dehydrogenase

decreases risk. Overlying areas of skin irritation, infection, or breakdown should be avoided. Mechanical ventilation is not a contraindication to thoracentesis.

Technique

All patients with pleural effusions should undergo a diagnostic and therapeutic thoracentesis, performed in a single setting. The rare exception exists, such as the patient with a typical presentation for congestive heart failure, but this is not the norm.

There are many commercially available thoracentesis kits on the market. Examples include the Arrow kit (Reading, PA, USA) and the Cardinal Health Kit (Dublin, OH, USA) (Fig. 56.1).

Patients are positioned in a sitting position, even those who are mechanically ventilated, if hemodynamically stable. (If not, they can be placed in a lateral decubitus position.) The patient may sit on a bed or a stool with his back easily accessible to the operator. The patient may use a table or gurney with a pillow in front to rest his arms and a stool beneath his feet. Unless loculated, pleural fluid will bow to the effects of gravity. Therefore, it is best if the back of the

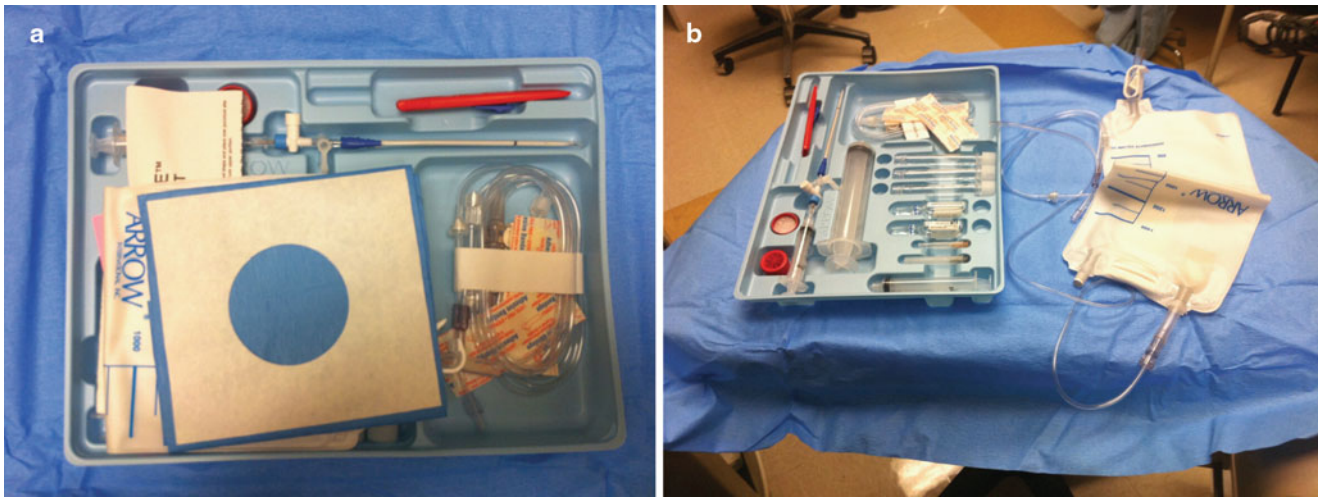

Fig. 56.1 Internal contents of a standard thoracentesis kit (*Arrow*, Reading, PA, USA): (**a**) Package with sterile drape inside; (**b**) Open kit with collection bag, needles, and specimen tubes

patient is as vertical as possible to best ensure the pleural fluid remains posterior. If not, the fluid may flow anteriorly, away from the operator who is positioned posteriorly. The height of the bed or chair should be adjusted to the height of the operator, who may perform the procedure sitting or standing, whichever is more comfortable. A procedure table to the operator's side holds the necessary equipment or kit. Once positioning has been completed, additional assistance is not typically needed, unless patient deconditioning prevents him from maintaining a sitting position with his own strength, in which case extra hands are needed.

The next steps are considered "safety steps." Prior to the initiation of the procedure and patient positioning, consent is obtained from the patient if able or from the health care proxy. Risks and benefits of the thoracentesis are clearly reviewed and documented in the patient's medical chart. With nursing or other medical staff in the room, a time-out is performed, ensuring the correct procedure is being performed on the correct patient and the correct side is being evaluated. The correct side, left or right, is also initialled by the physician performing the procedure.

After review of chest radiographs, physical examination is used to locate the best location to perform the thoracentesis. Decreased breath sounds are present over the pleural effusion, and there is a loss of tactile fremitus. Thoracentesis should be performed one intercostal space below where tactile fremitus is lost and percussion becomes dull. However, with the use of ultrasound at the time of thoracentesis, a more inferior space closer to the diaphragm may be more safely accessible. Thoracentesis is typically performed posteriorly, near the mid-scapular line or at least several inches lateral to the spine. The intercostal bundles, consisting of arteries, veins, and nerves, run behind and along the inferior margin of the rib, in the intercostal notch, along the posterior chest wall. Given this anatomy, needles and catheters accessing the pleural space should be placed on the superior margin of the rib, rather than inferiorly, to minimize potential complications.

Ultrasound guidance for thoracentesis has become a very useful tool and could be considered standard of care at this point. It should be used real time, not marked by a radiologist earlier in the day, with the thoracentesis then performed at a later time after the patient returns to the floor and has changed positioning. A significant reduction in pneumothorax risk has been shown (0 % vs. 29 % and 3 % vs. 18 %). It has also been used in successful drainage of pleural fluid after an unsuccessful clinically directed "dry tap" in up to 88 % of these patients. It increases the accuracy rate of thoracentesis by 26 %. It can also be used to predict the presence of trapped lung or lung entrapment, by evaluating lung motion and visceral pleural thickening (Fig. 56.2).

Once the patient is in the correct position and the best location for drainage has been marked, the skin is prepped either with chlorhexidine or betadine for sterilization, and a sterile drape is placed. There is no need to prep the entire back, only in and around the area of interest. Mask and sterile gloves should be worn as well during the procedure. Next, the skin and intercostal space is anesthetized; 5 mL of 1 % lidocaine without epinephrine is provided in the thoracentesis kits. A subcutaneous wheel should be made using a 25-gauge needle. Subsequently, this needle is replaced with a 22-gauge, 1–1.5-in. needle through the wheel, anesthetizing every 1–2 mm as it is inserted (drawing back on the syringe prior to each injection to ensure no intravascular placement) through the intercostal space directly above the rib into the pleural space. Once pleural fluid is aspirated, additional injection of lidocaine now mixed with pleural fluid is not recommended, as this could contaminate the intercostal space with infectious or malignant material. It is extremely difficult to anesthetize the parietal pleura, but if adequate anesthesia is provided along the track in the

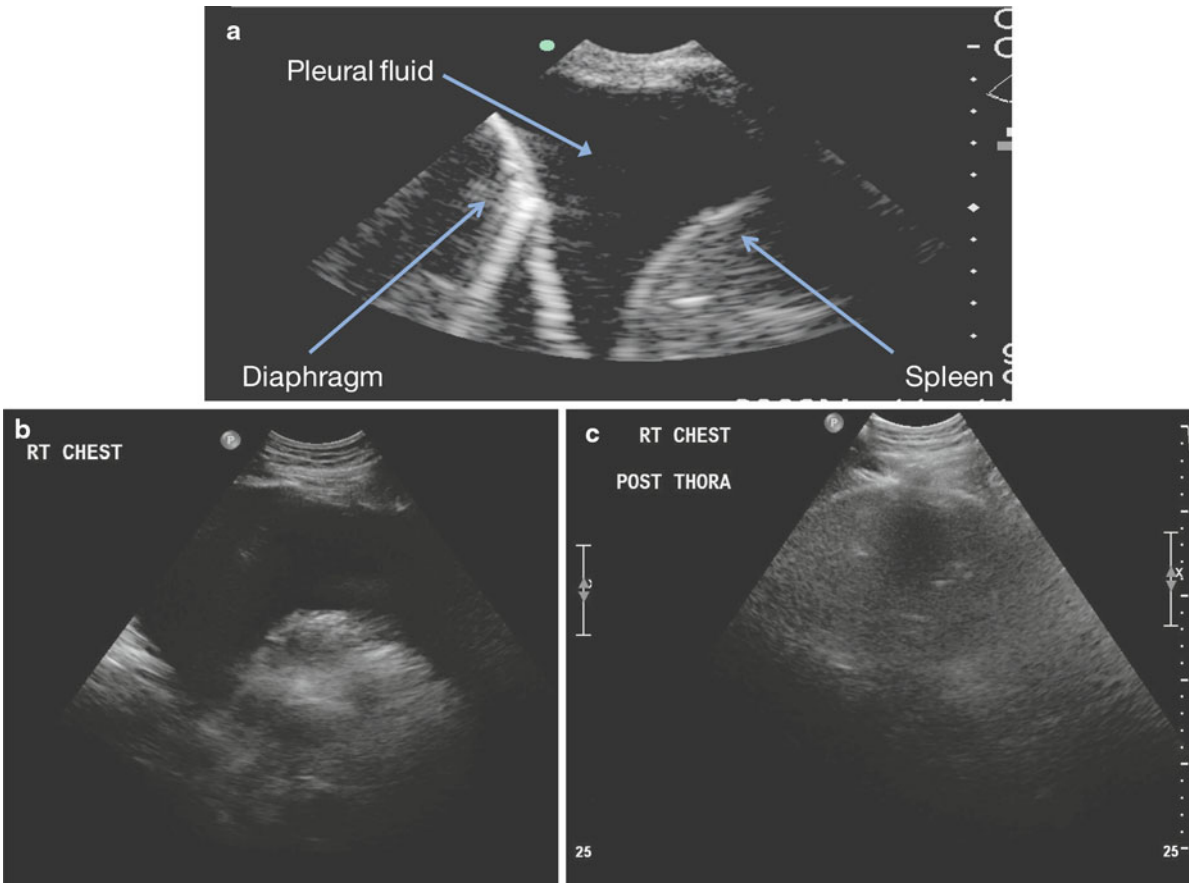

Fig. 56.2 Thoracic ultrasound: (**a**) Ultrasound demonstrating pleural fluid, diaphragm, and spleen; (**b**) Demonstration of pleural effusion prior to thoracentesis; (**c**) Post-thoracentesis

intercostal space, the patient should not feel discomfort during the remainder of the procedure.

After the anesthetizing or finder needle is withdrawn, a small stab incision using a #11 scalpel provided in the above kits is made subcutaneously. The needle with catheter is then inserted through the incision with constant aspiration from the attached syringe until pleural fluid is obtained. The catheter is then advanced over the needle into the pleural space and needle withdrawn. The needle is not advanced further as this increases the risk for complications, such as pneumothorax. Pleural fluid is aspirated using a one-way syringe and tubing until there is either lack of fluid or patient discomfort, exhibited with cough, anterior chest discomfort, referred ipsilateral shoulder pain, or shortness of breath (Fig. 56.3). Vacutainer (BD, Franklin Lakes, NJ, USA) bottles are not recommended as this increases the risk for reexpansion pulmonary edema (see below). Catheter is removed on an expiratory maneuver to ensure air is not introduced to the pleural space. This can be done by aspiration with the syringe or I have the patient hum if able. It should be timed with the expiratory cycle in mechanically ventilated patients. Site is then covered with sterile gauze to hold pressure in case of any bleeding and dry dressing placed. Post-procedure ultrasound can be performed to assess and document the remainder of pleural fluid (or lack of). Chest radiograph is not routinely done unless there is high suspicion of pneumothorax, such as aspiration of bubbles during the procedure, multiple attempts at fluid aspiration were unsuccessful, or patient has had other treatment to the thorax, such as radiation.

If fluid is not aspirated, one should ensure they are in the same line as the finder needle and catheter is not kinked. Assessment with thoracic ultrasound can be done if not done initially to confirm fluid.

Complications

Pneumothorax, while uncommon, is the most frequent complication of thoracentesis. It is significantly reduced in experienced hands and with the use of thoracic ultrasound. It can be caused by accidental laceration of the lung parenchyma. Bubbles will be seen in the syringe during the procedure. Air can also be introduced into the pleural space through the catheter during the procedure. This rarely results in a large pneumothorax, and air can be aspirated out of the space using a syringe. If the lung is trapped and unable to fill the vacated

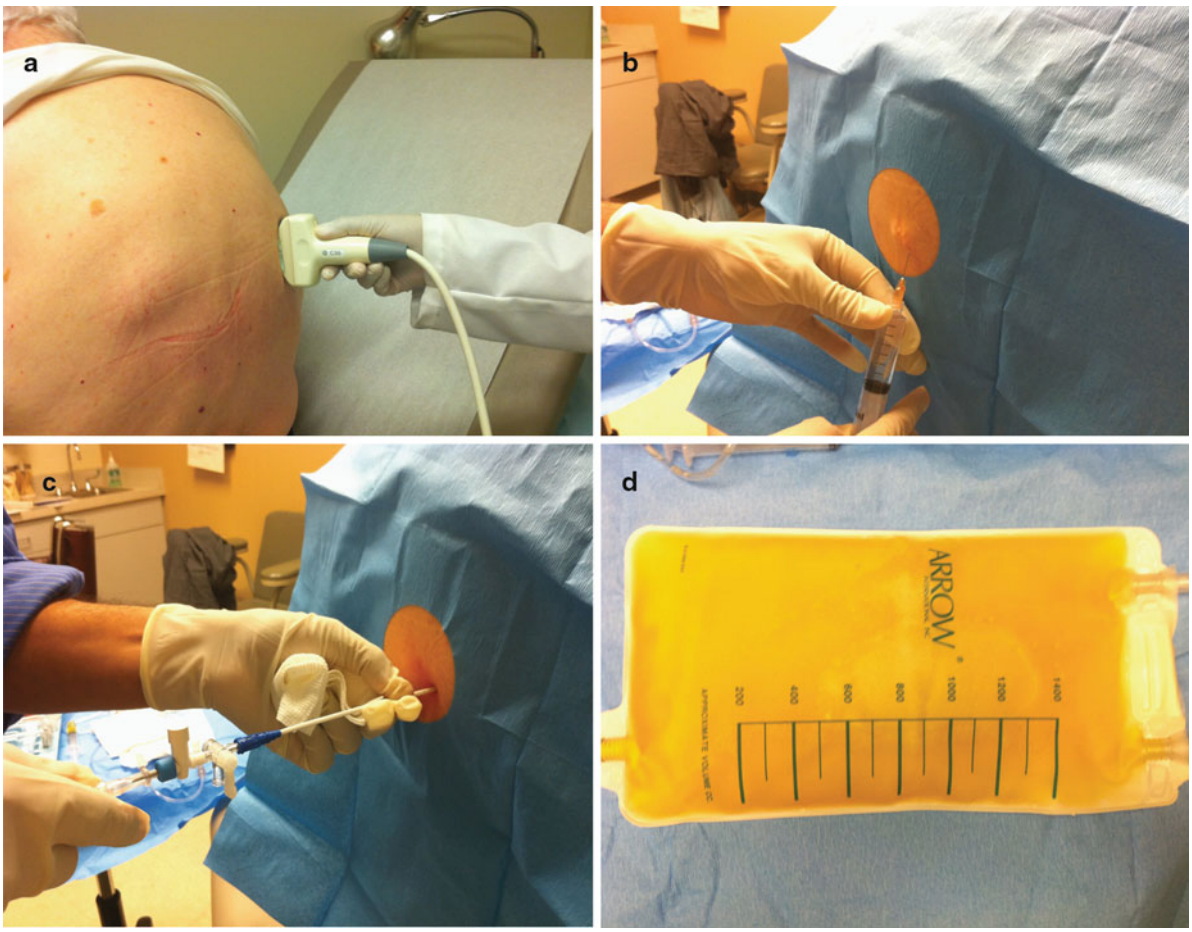

Fig. 56.3 Thoracentesis: (**a**) Chest ultrasound; (**b**) Skin anesthetization after sterile skin prep and placement of sterile drape; (**c**) Placement of thoracentesis needle and catheter; (**d**) Pleural fluid drained after thoracentesis

space after thoracentesis, it will appear as a pneumothorax on chest radiograph. This diagnosis can be suspected by discomfort during the procedure and decrease in pleural pressure on pleural manometry during the thoracentesis.

Vasovagal reactions can occur characterized by lightheadedness, diaphoresis, bradycardia, and hypotension. Rarely, loss of consciousness occurs. It can be triggered by anxiety, pain, or the sight of blood or the needle. When it happens, the procedure should be stopped and the patient placed in the supine or reverse Trendelenburg position to improve venous return and cardiac output. These symptoms are typically short lived.

Cough is common when large amounts of pleural fluid are removed. This is due to a change in intrathoracic and pleural pressures. If the cough becomes excessive, the procedure should be stopped. Pleural manometry can be measured during the procedure (see below) to assess intrapleural pressures. If dropping below −20 cmH_20, the procedure should be stopped, as intrapleural pressure below −20 cmH_20 places the patient at a much higher risk for reexpansion pulmonary edema (RPE).

Hemothorax is a rare complication but occurs secondary to laceration of an intercostal vessel. It should be suspected after a bloody tap and immediate reaccumulation of fluid on post-procedure thoracentesis. Laboratory analysis will reveal a drop in serum hemoglobin, and patient may exhibit hemodynamic instability, depending on the severity of the bleed. Surgical thoracoscopic evaluation may be required.

Fever after thoracentesis may indicate bacterial contamination of the pleural space, that is, a new etiology for the pleural effusion. Repeat thoracentesis should be performed to identify a possible new etiology of the effusion. Other uncommon complications include liver or splenic lacerations or soft tissue infection.

Drainage Volumes

Intrapleural pressure (Ppl) can be measured during a thoracentesis as a tool to assess risk for reexpansion pulmonary edema (RPE) and evaluate for lung entrapment and trapped lung. It is a measurement of pleural liquid pressure, in contrast to pleural surface pressure, which is the altering forces between visceral and parietal pleural surfaces. It is best to

place the thoracentesis catheter at the most dependent portion of the effusion, such that the pressure measured within the effusion will most accurately reflect the pressure within the pleural space. Increases in pleural fluid typically cause increases in Ppl. As the fluid is removed and the lung reexpands, Ppl should decrease and reach its steady state at FRC, −3 to −5 cmH_20. If the pleural pressure is negative, this can suggest trapped lung (from visceral pleural scarring, typically transudative, chronic, asymptomatic); if it starts out positive and drops quickly, this is more suggestive of lung entrapment (due to visceral pleural thickening, endobronchial obstruction, or interstitial disease, typically exudative, symptomatic).

When assessing risk for RPE with large-volume thoracentesis, measurement of Ppl is vital. Light and Feller-Kopman have looked at changes in Ppl during thoracentesis and pleural elastance (change in pressure divided by change in volume). Three curves were seen: (a) minimal change in pressure despite large volumes removed (normal pleural pressure), (b) normal initial pressure followed by a sharp drop (lung entrapment), and (c) negative initial pressure with a rapid drop (trapped lung). An initial pressure of less than −5 cmH_20 was only seen in patients with malignant effusions and trapped lung.

One would ideally like to drain as much fluid as possible during a thoracentesis to get the most relief of symptoms possible, to increase interval between possible additional procedures, to increase diagnostic yield, and to document lung reexpansion for possible later pleurodesis. Multiple studies have been performed evaluating the amount of fluid drained, symptoms, Ppl, and risk of RPE. It has been thought that a Ppl less than −20 cmH_20 places the patient at a higher risk. If aspiration is stopped when the Ppl reaches this level, RPE can be avoided. Light suggested stopping drainage at 1,000 mL as most operators are not measuring pleural pressures during the thoracentesis. Multiple studies since then have shown the ability to drain much larger volumes of pleural fluid without increased incidence of RPE if drainage is stopped if the Ppl drops below −20 cmH_20, there is no more fluid, or chest discomfort develops. RPE in these circumstances is very rare. Vacutainer aspiration should also be avoided as it is difficult to closely monitor the changes in pleural pressures.

Conclusions

Thoracentesis is a relatively safe procedure that can provide very useful information regarding a patient's pleural disease. It can also provide symptomatic relief. Risk is reduced dramatically with the use of real-time thoracic ultrasound at the time of the procedure. Large volumes can also be drained with minimal risk of pulmonary edema when monitoring for a change in pleural pressure, dropping below −20 cmH_20, or development of chest discomfort.

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Chest Tube Placement

57

Michael Klopp

Introduction

Tube placement or sampling of the pleural space is required when physiologic function of the respiratory and cardiovascular systems is threatened, as well as in diagnostic and therapeutic procedures (Table 57.1). If air, fluid or blood is accumulated in the pleural space, the sub-atmospheric pressure that keeps the pleural membranes apposed is nullified, and the intrapleural pressure becomes atmospheric or higher. The pleural membranes separate resulting in an enlargement of the pleural space, and a converse decrease in lung volume is seen. Buelau (1891) was the first who published reports describing both chest tube placements as well as the water ceiling (so-called closed chest tube system). Monaldi described the percutaneous intracavitary tube, which was placed anteriorly in the second intercostal space for post-infectious abscesses. Punctures for diagnostic sampling are done for examining gas or fluid collection or to define the best location for placing a chest tube. The placement of a pleural tube is often performed by multiple disciplines. It can be done safely in well-trained hands.

Physiology in the Pleural Space

The pleural space is defined by the space between the visceral and parietal pleura, which contains a small amount of fluid generating a mechanical connection of the lung with the chest wall, due to their passive and elastic structure.

The intrapleural pressure alternates during a breathing cycle in between −8 cm H20 (inspiration) and −2 cm H20 (expiration). Forced inspiration and expiration lead to a pressure difference of −54 cm H20 to + 70 cm H20. However, the negative intrapleural pressure cannot be sustained when fluid or gas enters the pleural space. That, in the absence of pleural adhesions, results in a collapse of the lung with hypoxemia and alveolar hypoventilation. If the pressure in the pleural space increases to a tension pneumothorax, shifting of the mediastinum to the contralateral lung and decrease venous flow of blood back to the heart can result in severe hypoxemia and hemodynamic collapse. By insertion of a chest tube, draining of the pleural space and restoration of the physiologic pressure conditions can be obtained.

Indications for Chest Tubes

The initial therapy for every *symptomatic pneumothorax* is the immediate placement of a tube. Diagnostic workup has to be postponed when clinical symptoms and signs of pneumothorax start to be life threatening. One exclusion to this rule is selected cases with primary (idiopathic) spontaneous pneumothorax (PSP) or asymptomatic partial PSP (pneumothorax, with a pleural separation < 1 cm). These patients can be observed under close surveillance. In an emergency with a symptomatic tension pneumothorax, when a regular chest tube placement cannot be achieved in time, intercostal puncture with a wide lumen indwelling catheter can result in a temporary release of the life-threatening situation. In patients under mechanical ventilation, developing pneumothoraces make chest tube placement almost always mandatory. These patients can quickly establish a tension pneumothorax.

In iatrogenic pneumothorax, after transbronchial biopsy, transthoracic needle aspiration or paravertebral nerve blocks (pain therapy) or after puncture of the V. subclavia (central venous catheter), a lung parenchyma injury with pneumothorax may develop. After every procedure, a chest X-ray should be performed. After minor interventions, asymptomatic pneumothoraces with small apical separations can be frequently observed. In these patients, close observation is recommended as these pneumothoraces can progress.

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Table 57.1 Indications for chest tube insertion

• Pneumothorax
◦ Tension pneumothorax (idiopathic, traumatic pneumothorax with valve mechanism, etc.)
◦ Pneumothorax on mechanical ventilation
◦ Persistent or recurrent iatrogenic pneumothorax after needle aspiration
◦ Symptomatic pneumothorax
◦ Large pneumothorax
• Malignant pleural effusion
• Empyema (stage-dependent) and complicated parapneumonic effusions
• Traumatic hemothorax secondary to chest trauma
• Post-operative care (e.g. after thoracotomy, video-assisted thoracoscopy, coronary bypass)

Source: Data from Klopp M, Hoffmann H, Dienemann H. Pleural drainage. Dtsch Med Wochenschr. 2009;134(11):536–539

In patients with *hemothorax*, *it is essential to* evaluate the degree of bleeding. Inserting a chest tube can facilitate re-expansion of the lung and may avoid trapping of the lung as well as late empyema development.

The situation of *parapneumonic fluid* collection is controversial. Does it need a tube placement? Commonly accepted is the tube placement in stage II empyema (ATS-Classification 1962). Tube placement in a stage I empyema with residual fluid or not fully expanded lung can help drain the pleural cavity and assist full lung expansion.

In symptomatic or recurrent malignant *pleural effusion*, an insertion of a chest tube is indicated because of diagnostic and palliative reasons, as well as in cases in which a pleurodesis is considered.

Contraindications for Chest Tube Insertion

Absolute contraindications do not exist. Relative contraindications are found in patients with bleeding disorders or anticoagulation therapy. Special conditions include pleural adhesions, loculated pleural effusions or empyema, pulmonary giant bullae – misinterpreted as pneumothorax – and, in trauma patients, rupture of the diaphragm with thoracic displacement of intra-abdominal organs. Under these circumstances, computed tomography or ultrasound should be applied, and the operating room should be in standby.

Patient Consent

The patient has to be informed about indication, technique and impact on their health condition. The use of local anaesthesia as well as the possibility for additional sedation should be mentioned. In addition to the general information sheet, every possible complication should be explained and described, and especially the following ones should be mentioned:

- Improper placement
- Tube dislodgement
- Organ penetration with bleeding, bronchopleural fistula
- Empyema – chest tube placement could introduce bacteria into the pleural space
- Re-expansion (oedema) of the lung with coughing, shoulder and thoracic pain as well as vagal reactions
- Injury to the intercostal blood vessels/nerves and the periosteum of the rib with bleeding, pain and intercostal neuralgia
- Injury of intraperitoneal or intrathoracic organs
- Emergency thoracotomy
- Need for additional procedures

Sizing of Chest Tubes on the Basis of Indication

Appropriate are silicone tubes in a size between 6 and 32 French with length marking, contrast line and multiple side perforations. Straight and right-angled tubes are available. The size of the tube that is needed depends on the indication for the chest tube insertion (recommended sizes for pneumothorax are 20 Fr, 24–28 Fr for effusion), as well as considerations for gender and size of the patient.

Preoperative Diagnostic Workup

The insertion of the chest tube has to be done after accurate clinical examination and after review of the X-ray, chest CT or ultrasound. The only exclusion is the urgent, clinical suspicion of a tension pneumothorax with loss of blood pressure, hypoxemia, tachypnoea, superior vena cava syndrome and high ventilation pressures.

Pleural Chest Tube Insertion

Position of the Patient, Anatomy, Anaesthesia and Technique

The insertion of the chest tube has to be done under sterile conditions with special instruments (Fig. 57.1). In the situation of non-loculated processes, the insertion should be done in supine position or at an angle of 45°; the arm on the affected side should be abducted and externally rotated.

The third to fifth intercostal spaces in the anterior to midaxillary line should be chosen in a pneumothorax. For orientation, in male patients, the nipple line or the submammary fold in female patients can be used (fourth intercostal

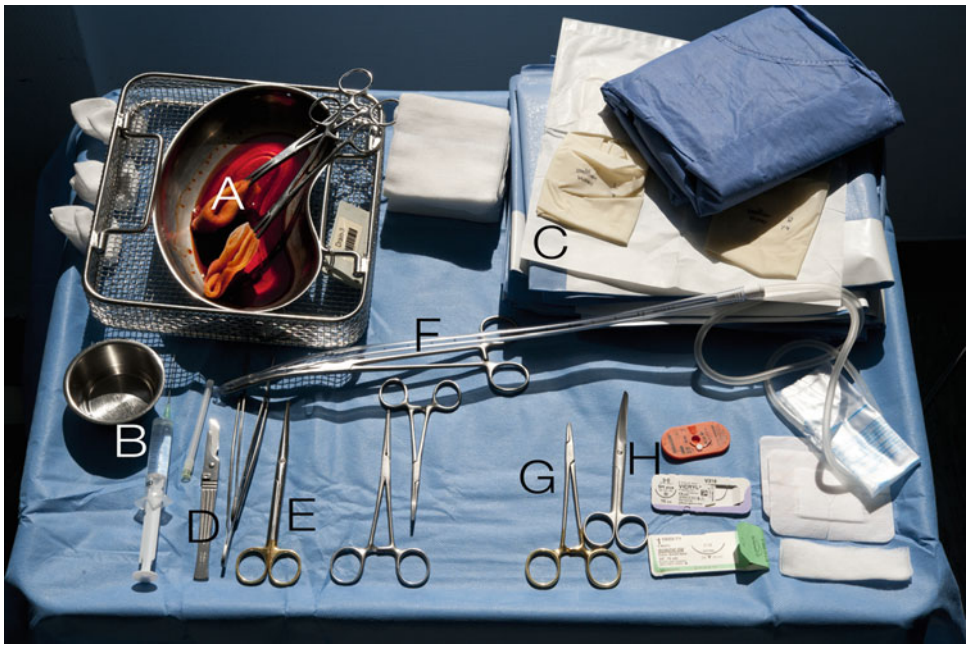

Fig. 57.1 Instruments: (**a**) Disinfectant, (**b**) Local anaesthesia, (**c**) Sterile drapes, (**d**) Scalpel and forceps, (**e**) Scissors, (**f**) Pleural drainage and Kelly clamp, (**g**) Needle clamp, (**h**) Scissors and suture

space). The safest and least traumatic position is the muscle-free triangle between the M. pectoralis major and the M. latissimus dorsi. No further muscle besides the intercostal musculature has to be perforated. In addition, the resulting scar is well positioned from a cosmetic perspective, and kinking of the tube can be avoided. Loculated processes require a targeted insertion, sometimes under CT or ultrasound guidance.

The second intercostal space in the midclavicular line (Monaldi position) is recommended sometimes. The advantage is the easy orientation in a recumbent patient (insertion of the second rib at the level of the angulus sterni is easy to identify). Disadvantages are as follows:

(a) Perforation of the M. pectoralis major – high risk of bleeding
(b) Difficulty in placing the tube apical or basal
(c) Risk of kinking the tube in recumbent patients
(d) Unfavourable cosmetic outcome after removing

Even more inappropriate is the posterior insertion medial to the scapula. This placement is used for dorsal localised processes.

Anaesthesia and Technique (Step by Step)

1. Disinfect and apply sterile drapes to the area.
2. The most appropriate site for chest tube placement (in PSP) is the fourth or fifth intercostal space in the mid- or anterior axillary line (Fig. 57.2a).
3. Administer analgesia (unless contraindicated): 10–20 ml of local anaesthetic solution subcutaneous, pericostal, intercostal with anaesthesia of the pleura parietalis and aspiration of air or fluid (Fig. 57.2b), so that an adequate position for tube insertion is identified.
4. Make a skin incision approximately 2 cm long overlying the rib in the same direction as the rib itself; bluntly dissect the subcutis and musculature of M. serratus (Fig. 57.2c), oriented along the superior border of the rib. Penetrate carefully the intercostal musculature and the pleura either with a short scissor (closed while invading and open while pulling back) or with the sterile finger (Fig. 57.2d). Now the trapped air or fluid can escape.
5. Do digital palpation to feel lung tissue and possible adhesions. Rotate the finger 360 to appreciate the presence of dense adhesions (Fig. 57.2d).
6. Bluntly insert the tube (without trocar!!!) with a Kelly clamp in a dorso-apical direction or dorso-caudal in the case of effusions (seropneumothorax)
7. If placed correctly, very little resistance should be felt. An elastic resistance is sometimes seen in cases of kinking tubes, and the tube should be repositioned. If the tube demonstrates kinking outside the thorax, a false path (Fig. 57.2e) outside the osseous thorax was taken.
8. Draining of air in the thorax, the tube fogs up with every single expiration. The patency of the system can be seen with synchronised fluctuation of the fluid in the tube or of the fluid level in the collecting container with respiration. A sign for a fistula in the lung parenchyma is if

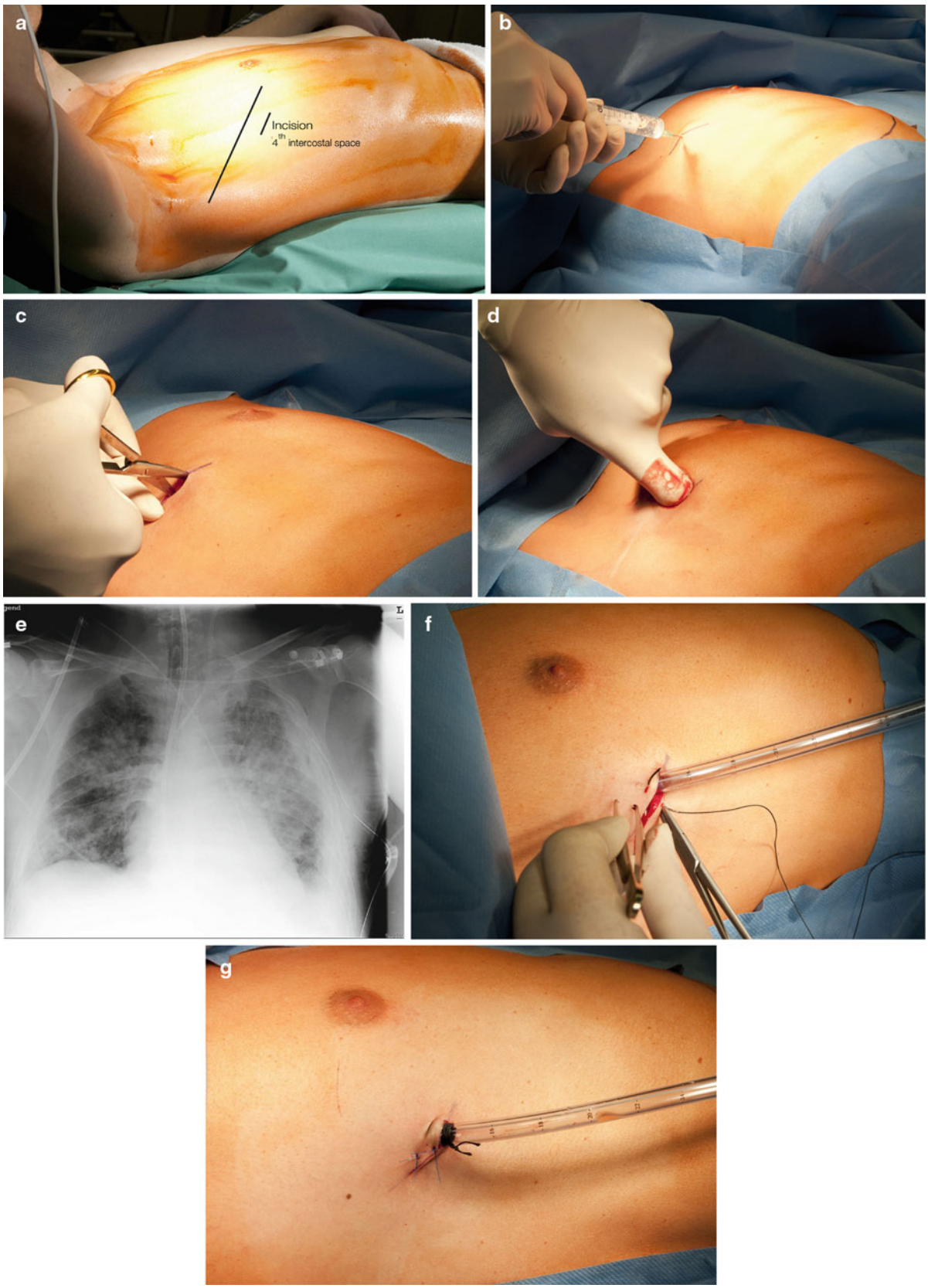

Fig. 57.2 (**a**) Favoured insertion site for a chest tube (in PSP) is the fourth/fifth intercostal space in the anterior or midaxillary line. (**b**) Local anaesthesia and aspiration of air. (**c**) Bluntly dissect the subcutis and musculature, oriented along the superior border of the rib. (**d**) Penetrate carefully the intercostal musculature and the pleura with the sterile finger. (**e**) Malposition of the chest tube outside the osseous thorax. (**f**) The tube should be fixed with a strong suture via U-suture technique. (**g**) The fixation suture should be tied, so that it can be used for closing after removing the tube

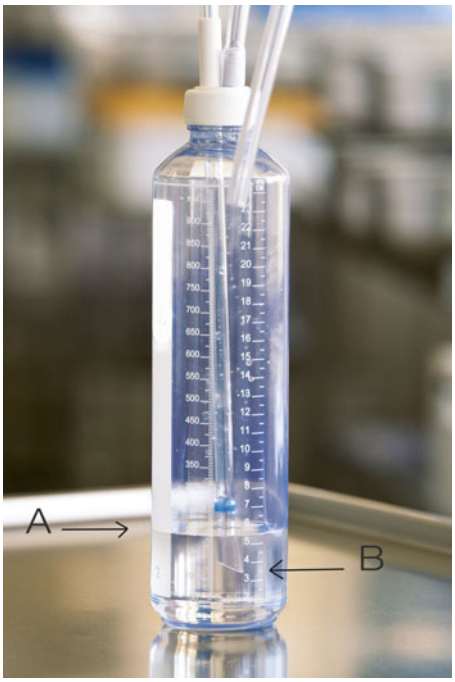

Fig. 57.3 "Passive" systems with collecting container ("Bulau concept" 1891). A partially water-filled container is the collecting container as well as the valve. The water seal functions as the valve during inspiration. (**a**) 200-ml distilled water; (**b**) Seal function

there is air leak synchronised with respiration and no leakage can be found in the system.

9. After making sure that the system is patent and the tube is correctly placed, the tube should be fixed with a strong suture via U-suture technique (Fig. 57.2f, g) (air and fluid tight). The fixation suture should be tied, so that it can be used for closing after removing the tube (single knot then twisting around the tube, multiple final knots).
10. Have a sterile connection of the tube with the collecting container, so-called Bulau concept (Fig. 57.3); if necessary, you can connect a suction system with −15 cm H20 to the tube system.
11. For documentation of the correctly placed tube and re-expansion of the lung, a chest X-ray (PA and lateral) should be performed.

Management of the Tube System

If possible, a PA and lateral film should be obtained to document the position of the tube or demonstrate malposition requiring revision if necessary. The position in between the lung fissures is not necessarily misplacement, as long as there is adequate draining. The length of the tube should always be as short as possible so that no loops occur, but the patient should be able to move freely. If the tube is too long, the resistance for fluid is increased, and this may cause blood or fibrin clotting. Most frequently, the narrowing at the connector is the reason for occlusion. Manipulation of the tube should be avoided for preventing contamination of the pleural space via the tube. Clots should be removed via an aseptic suction system.

The patency of the system can be seen via breathing synchronised movement of the fluid in the tube or in the collecting container. Considerable variation indicates a none fully expanded lung. A breathing synchronised air leak can indicate either a leakage in the system or a parenchyma fistula.

Tube Systems

"Passive" systems result in drainage of fluid or air during expiration but prevent entrainment of air and fluid during inspiration. The underwater seal drainage system of Bulau is recommended. A partially water-filled container is the collecting container as well as the valve (Fig. 57.3). The water seal functions as the valve during inspiration. The simplest system is the "Heimlich" valve. This can be connected directly to the tube in cases of simple pneumothorax. This also can be used in outpatient patients with persistent air leak.

"Active" tube systems depend on the additional negative pressure principle. It is necessary in delayed re-expansion because of several indications. High-volume, low-pressure suction is recommended (−15 to −30 cm H20). If the lung is not expanding, the negative pressure can be contra productive and maintain a parenchyma fistula.

Post-operative Treatment and Tube Removal

For post-operative analgesia, NSAIDs (unless contraindicated) are adequate. They can be supported by opioids (see WHO scheme for pain therapy). Immediate mobilisation of the patient is necessary.

The removal of the tube is indicated after full expansion of the lung, resolution of the air leak or after healing of the empyema. But the individual situation is very important, especially if the pleural space is contaminated. Clamping before removal is in general not necessary, except after a long-lasting fistula for confirmation of the expansion situation.

General or local anaesthesia is not necessary for removing the tube. The patient should inspire deeply followed by a Valsalva manoeuvre. The tube should be removed during the Valsalva phase. The insertion site should be closed via the U-suture tightly. After 24 h, a chest X-ray is obligatory for documentation.

Caution! A chest tube demonstrating an air leak should never be clamped or removed.

Intraoperative Complications

Misplacement

A tube placed too deep with pressure against the pleura can cause back or shoulder pain by irritating the parietal pleura. Too short insertion (extrathoracic position of the side holes) or insufficient fixed tubes can demonstrate tissue emphysema in pneumothoraces.

Injury of Organs

Especially when using a sharp metal trocar for insertion, the parenchyma can be injured. The trocar tubes are, especially for young, inexperienced physicians, not recommended. Penetration of the lung, spleen, liver, heart, stomach, great vessel as well as diaphragm can be potentially fatal. The risk of injury can be heightened when the diaphragm is elevated due to paresis of the phrenic nerve, the obese patient in supine position and after pneumonectomy.

Bleeding

A small degree of bleeding often stops spontaneously. Injury of the intercostal artery can cause large-volume bleeding. This can be avoided by using the correct insertion technique above the rib. Profuse bleeding indicates direct injury of great vessels (aorta, V. cava, pulmonary artery, heart) – or a hemothorax after trauma or surgery. Incorrect placement results in this rare complication.

Tangential injury of the diaphragm can cause fatal bleeding. Transdiaphragmatic injury of abdominal organs has to be considered in cases of an acute abdomen or hemorrhagic shock.

Post-operative Complications

Fistula and Tissue Emphysema

The presence of tissue emphysema should trigger a check of the tube position, patency and tightness of the connections. Wide broncho- or alveolo-pleural fistulas can result in tissue emphysema, if the tube system is too small. In these cases, an active system should be used. If there is bloody foam, there is usually a direct parenchymal injury with associated bleeding and air leakage. Very often, a second tube or a surgical revision is necessary.

Wound Infection and Empyema

The insertion site can cause a local wound infection. In most cases, conservative management is sufficient. In cases of primary sterile insertion in a sterile pleural space, empyema should not be expected after full lung expansion. Only in patients with co-morbidities and other risk factors, single-shot prophylactic antibiosis is recommended. In patients with long-lasting lung fistulas and the risk for the development of post-interventional empyema, early surgical revision should be considered.

Re-expansion Oedema

Unilateral re-expansion oedema is a rare but potentially lethal complication. Patients at high risk are patients with long-term total atelectasis of the lung and with rapid re-expansion. The clinical symptoms are strong irritation of the throat, production of light red sputum, tachypnoea and tachycardia. X-ray findings demonstrate unilateral lung oedema that can occur within 24 h after re-expansion.

Intercostal Neuralgia

A direct injury of the periosteum can be avoided by correct anatomic knowledge. Very often, the intercostal nerve can be irritated. This can warrant analgesic therapy or repeated local anaesthetic infiltration.

Essentials in Brief

- Before chest tube insertion, check the indication and surgery side via chest X-ray
- Favoured insertion site for a chest tube (in PSP) is the fourth/fifth intercostal space in the midaxillary line
- After spreading the pleura, blunt palpation of the pleural space should be performed to look for adhesions and confirm intrapleural position
- Chest tube removal, just after resolution of fistulas and after fully expanded lung, should be documented via X-ray.

Suggested Readings

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Small-Bore Drains and Indwelling Catheters

58

Saleh Alazemi

Introduction

Pleural effusion affects 1.3 million individuals each year with a relative annual incidence estimated to be 320 per 100,000 people in industrialized countries. Pneumothorax is relatively less common with an annual incidence ranging from 1.2 to 26 per 100,000 population per year, depending on the patient's sex and underlying etiology.

Insertion of chest tubes into the pleural space represents the traditional approach to draining the pleural space. Chest tubes vary in size and can be classified as large-bore (24–34 F) or small-bore (8–24 F). The size of the catheter is usually dictated by the underlying indication for the catheter insertion, with larger catheters usually preferred to drain more viscous pleural collections such as blood and pus. Traditionally, large-bore drains were inserted for pleural drainage; however, over the past decade, there has been a move toward inserting small-bore chest catheters (SBCCs). The reasons for this include a perceived reduction in patient discomfort and invasiveness and the apparent ease and speed of insertion of SBCC.

Large-bore chest tubes are usually inserted without imaging guidance by a "blind" technique where the chest wall is penetrated through a blind dissection or with the use of a trocar. On the other hand, SBCCs are usually inserted under imaging guidance using the Seldinger technique. Various imaging modalities, such as fluoroscopy, ultrasonography (US), or CT imaging, are available. Sonography is the technique of choice to guide SBCC placement for pleural drainage. Its advantages include absence of ionizing radiation, portability, and real-time capabilities. In addition, pleural drainage can be performed at the bedside using sonographic guidance in critically ill, hemodynamically unstable patients.

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In this chapter, we will discuss the indications, insertion techniques, and complications associated with image-guided insertion of SBCC using the Seldinger technique. The literature will also be reviewed to compare their use with the traditional large-bore chest tubes.

Small-Bore Chest Catheters

SBCCs have evolved significantly over the past decade (Fig. 58.1). They are made of softer and more flexible material than the standard large-bore chest tubes. This results in considerably less pain and discomfort for the patient and makes them easier to secure to the chest wall. There are many types of SBCC kits that are available commercially. Catheters ranging from 8.0 to 28.0 F are available for insertion over a guidewire, but the most commonly used catheters range in size between 8.0 and 16.0 F. Some of the catheters have a curved end in a pigtail configuration, hence the name "pigtail catheter" (Fig. 58.2). This feature serves as an internal locking mechanism that provides some measure of protection against inadvertent catheter dislodgement by an uncooperative patient or during patients' transportation. The choice of catheter size is based on the viscosity of the fluid to be drained. A small 8–12 F catheter may be sufficient to perform a simple thoracentesis or to drain a free-flowing transudative pleural effusion. However, for more viscous effusions, such as complicated parapneumonic effusions, empyema, and hemothorax, tube occlusion commonly occurs with smaller catheters, and most interventionists usually start with catheter size 16 F and above.

Image Guidance

Imaging of the pleural space is a vital part of pleural intervention. It gives an initial idea about the viscosity of the pleural fluid and the complexity of the pleural space, which helps in the pre-procedure planning such as choosing the appropriate SBCC size and the entry site. In addition, if the

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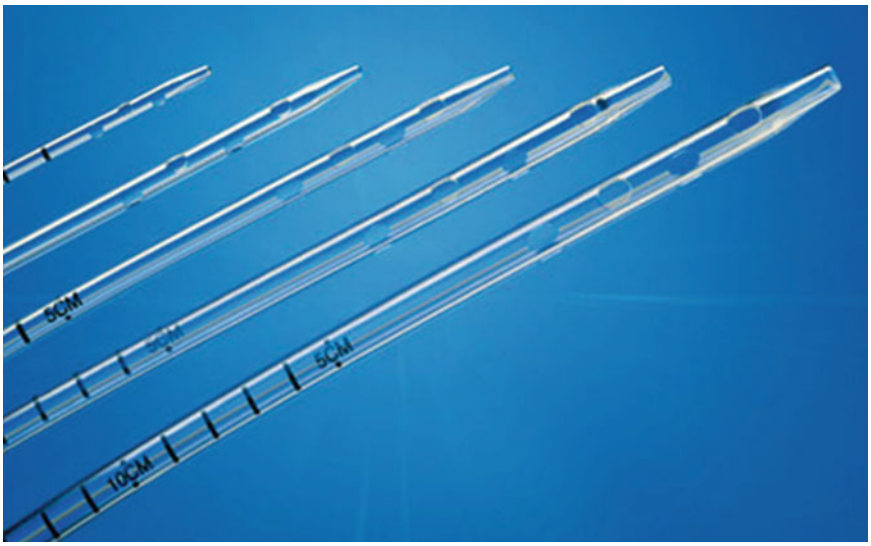

Fig. 58.1 Small-bore chest catheters of different sizes

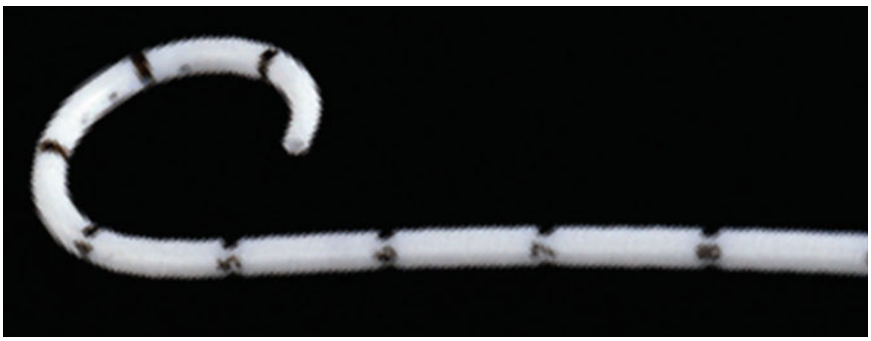

Fig. 58.2 Pigtail catheter

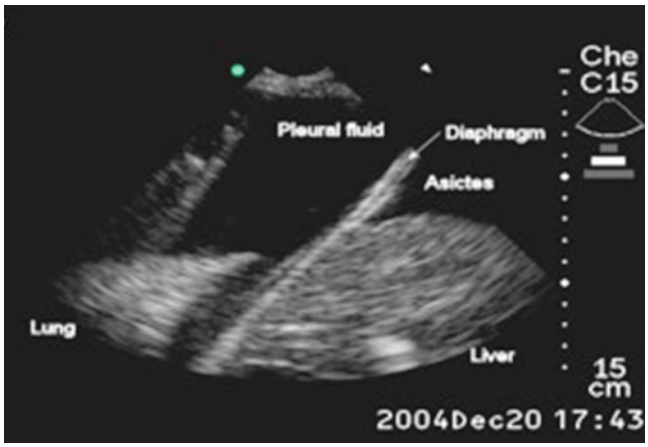

Fig. 58.3 Portable ultrasound machine (M-turbo, SonoSite, Inc., USA)

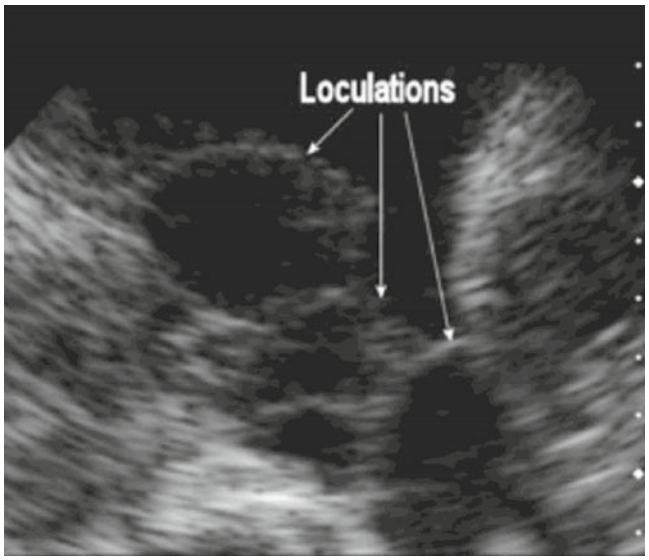

Fig. 58.4 Loculated pleural effusion

parietal pleura is seen to be thickened and inflamed, one would anticipate a rough catheter introduction and thus may apply more generous local anesthesia to avoid patient's pain and discomfort. During the procedure, image guidance helps to avoid catheter malposition in relation to fluid loculations. By using modern cross-sectional guidance techniques, primarily CT and ultrasound (Fig. 58.3), it is relatively easy to place the drainage catheters into specific loculations of fluid regardless of the size or location of the collection (Fig. 58.4).

Finally, in case of multiple loculations, several catheters can be placed at the same setting under image guidance. This is the single most significant advantage of image-guided over non-guided thoracostomy, and its importance should not be underestimated.

Indications

Pleural Space Infection

Pleural space infections are associated with considerable morbidity, mortality, and health care resource use (Table 58.1). Drainage of the pleural space is the key component of care; however, the modality and extent of drainage and debridement has long been debated. Options include nonoperative (thoracentesis and tube thoracostomy with or without intrapleural thrombolytic therapy) and operative (thoracotomy or VATS) intervention. The approach to pleural space infection varies significantly between physicians reflecting differences in specialization, access to thoracic surgeons, and conventional wisdom and training.

The usual argument against the use of chest tubes for pleural space infection was the high incidence of loculation within the pleural space that usually impairs chest tube drainage and prevents complete evacuation of the pleural space. However, with image-guided SBCCs, this argument may not stand anymore. SBCCs offer many advantages over the traditional chest tubes for the management of pleural space infection. First, in case of loculated pleural effusion, SBCCs can be accurately placed exactly in the desired fluid pocket. Second, in the presence of multiple loculations, several SBCCs can be placed in the same setting. Finally, in the case of numerous loculations, the use of intrapleural thrombolytic agents might be useful to break the loculation and improve the drainage.

It is unclear how the growing availability of new management options for pleural drainage has affected clinical practice in the community at large.

Table 58.1 Selected indications for SBCC insertion

Indication
1. Pneumothorax
All patients on mechanical ventilation
Hemodynamic instability
Secondary spontaneous pneumothorax
Large and symptomatic iatrogenic pneumothorax
Large, recurrent, or persistent primary spontaneous pneumothorax
Secondary to chest trauma
2. Hemothorax/hemopneumothorax
3. Complicated parapneumonic effusions/empyema
4. Malignant pleural effusion
5. Persistent or recurrent symptomatic pleural effusions
6. Pleurodesis for symptomatic persistent effusions, usually malignant
7. Intrapleural thrombolytic therapy for complicated parapneumonic effusion/hemorrhagic effusions
8. Bronchopleural fistula
9. Chylothorax
10. Pleural effusion secondary to esophageal rupture
11. Postoperative care (after coronary bypass surgery, thoracotomy, or lobectomy)

Malignant Pleural Effusions

Malignant pleural effusions (MPE) develop in patients with a variety of malignancies with lung and breast carcinomas and lymphomas accounting for about 70 % of all malignant effusions. Several management options exist for patients with MPEs and depend on how symptomatic the patient is, the rate of fluid reaccumulation, the presence of trapped lung, patient's prognosis, and anticipated tumor response to the available treatment. Asymptomatic patients with slowly reaccumulating pleural effusions may benefit from repeated thoracentesis. However, for a patient in whom the pleural effusions reaccumulate rapidly, this option might be bothersome. In such patients, insertion of SBCC serves several purposes. It helps to completely drain the effusions, which is important to assess the lung expansion and to rule out lung entrapment that will affect the decision for further long-term management plans. If lung entrapment is ruled out, then pleurodesis is an effective method for long-term control of the effusion. Conventional large-bore chest tubes (24–32 F) have been traditionally employed in most studies involving sclerosing agents because they are thought to be less prone to obstruction by clots. However, their placement is perceived to be associated with significant discomfort. SBCCs offer similar efficacy and less pain and discomfort to the patients. Studies using SBCCs with commonly used sclerosants have reported similar success rates to large-bore chest tubes.

Pneumothorax

Pneumothorax can be classified as spontaneous or iatrogenic. Spontaneous pneumothorax can be subdivided into primary, in patients with no underlying lung disease, or secondary, which is associated with parenchymal lung disease. Traumatic pneumothorax results from chest trauma or as an iatrogenic complication of thoracentesis, transthoracic needle lung biopsy, transbronchial lung biopsy, or central venous line insertion.

The optimal size for chest tube needed for pleural aspiration in cases of pneumothorax is usually determined by the rate of air leak. In patients who are not at risk for large air leak (e.g., spontaneous and iatrogenic pneumothorax), SBCCs may be sufficient to maintain adequate air evacuation. However, patient with impending tension pneumothorax, underlying

severe lung disease, receiving mechanical ventilation, or in cases of traumatic pneumothorax especially in combination with hemothorax, larger conventional chest tubes may be required for adequate evacuation of the pleural space.

Hemothorax

In general, large-bore chest tubes are the preferred approach in the management of hemothorax in the acute phase. However, after the acute phase has resolved, septation may form and prevent complete evacuation of the pleural space by the chest tube. In such conditions, SBCCs may be inserted under image guidance into the specific pockets and may avoid patients from further surgical intervention. In case where mature blood clots form, however, surgical intervention might be the only option to completely evacuate the pleural space.

SBCC Insertion

Insertion Site

With the traditional large-bore chest tubes, most clinicians insert the chest tube via an incision at the fourth or fifth intercostal space in the anterior axillary or midaxillary line where the tube then advanced blindly either apically or posteriorly depending on the underlying nature of the pleural disease. With this method, tube malposition can occur, especially in cases of loculated collections. Image-guided SBCCs overcome this problem by allowing the physician to accurately place the catheter exactly into the pleural collection (Table 58.2).

A thorough examination of the chest with an appropriate imaging modality (usually US) is first performed. In cases of free-flowing effusion, the entry site is preferred to be as lateral as possible to avoid patient discomfort and tube dislodgement when the patient lies supine. In addition, the entry site is preferred to be as inferior as possible and then advanced posteriorly to the most gravity-dependant region of the pleural space to allow for maximum drainage. Insertion of catheters medial to the scapula is discouraged unless absolutely necessary because it carries the risk of catheter dislodgement with scapula movement. However, in cases of loculated collections, the entry site should be marked exactly at the site of the collection (preferably at the inferior border of the collection) seen on the US. In cases of pneumothorax, the entry site is usually chosen in the anterior chest wall, usually in the second intercostal space.

Types of SBCC

Many SBCC kits are commercially available. When choosing an SBCC kit, several things should be considered. The

Table 58.2 SBCC insertion

Review indication and contraindication for the procedure including risk benefit ratio
Review relevant imaging (CXR, CT scan, US imaging)
Explain the procedure to the patient and make an informed consent
Insure all necessary equipment are available
Insure that the patient is monitored throughout the procedure
Place the patient in supine or semirecumbent position with the ipsilateral arm maximally abducted or place behind the head
Examine the ipsilateral thorax with ultrasound machine and choose and mark safe entry site
Use full sterile barrier precautions (hand wash, sterile gown and gloves, protective eyewear, and a face mask)
Create a large, sterile field on the patient's skin, using sterile gauze and 2 % chlorhexidine solution
Drape the patient, exposing only the marked area
Apply local anesthesia 1 % or 2 % lidocaine solution First, infiltrate the skin with 25-gauge needle to create a wheal at the previously marked entry site Use larger needle (21-gauge) to apply anesthesia to the deeper tissues including subcutaneous tissue, periosteum, and parietal pleura
Using continuous negative suction as the needle advances, confirm entry into the pleural space when a flash of pleural fluid enters the syringe
Inject the rest of lidocaine into the pleural space to anesthetize the parietal pleura and then withdraw the needle
Repeat steps 12 and 13 using the introducer needle. Once in the pleural space, remove the syringe and introduce the guidewire. Direct the needle apically (for pneumothorax) or inferiorly (for pleural effusion) to guide your wire into the desired target
Remove the needle with the guidewire in place (remember: never let go the guidewire)
Make a small (0.5 cm) incision at the entry site
Introduce serial dilators over the guidewire to dilate the subcutaneous tissue and the parietal pleura
Introduce the SBCC over the guidewire. Insure proper placement by aspirating fluid or air through the SBCC
Connect the SBCC to the drainage system, secure it to the skin, and place proper dressing on
Obtain CXR to confirm placement

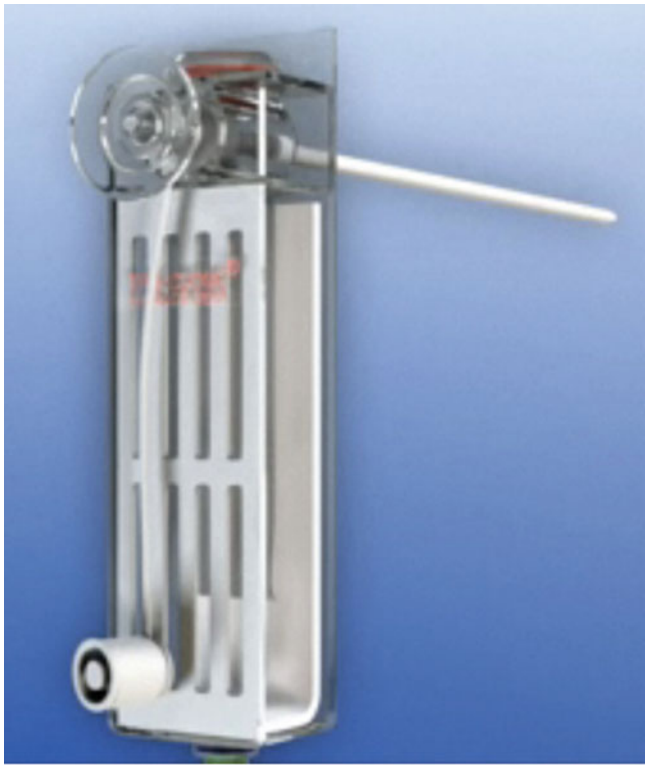

Fig. 58.5 Tru-close thoracic vent. UreSil, Skokie, IL

catheter should be made of soft and flexible material to allow for easy navigation and placement through the intercostal space and to minimize pain and discomfort to the patients. Catheters with coiled ends (pigtail configuration) are preferred for prolonged drainage of pleural effusion (e.g., malignant effusions and parapneumonic effusions) as they provide an additional locking mechanism that minimizes the chance of catheter dislodgement (Fig. 58.2). The catheter should be radiopaque, so it can be easily identified on chest radiographs. Finally, catheters should have sufficient side holes to allow for adequate drainage and minimize catheter blockage.

In general, most of SBCCs used for pleural effusions are inserted with the Seldinger technique. However, for small pneumothoraces with small air leak, a compact, one-piece pneumothorax drainage system is available (Tru-Close Thoracic Vent. UreSil, Skokie, IL). This unit is composed of a 12- or 13-French, 10-cm-long catheter connected to a rectangular chamber that contains a self-sealing aspiration port, a red signal diaphragm indicating entry into the pleural space, and a flutter valve (Fig.58.5).

As most of the currently available kits fulfill all of the above criteria, one should choose the kit that he is most comfortable with. Using multiple kits usually cause confusion and may prolong procedure time especially in cases of emergencies.

Preparation

Prior to SBCC placement, all available imaging should be carefully reviewed. This allows the operator to have an idea about the pleural space anatomy and the expected size and location of the pleural collection. In addition, one should insure presence of enough pleural space for a safe insertion of the catheter using the Seldinger technique without injuring the lung parenchyma.

Patient is then placed in the desired position which varies among clinicians. However, most interventionists prefer to place the patient in the supine position with the ipsilateral arm over the head. Sometimes, a lateral decubitus position is necessary to gain access to a posteromedial fluid collection. In patients with a collapsed lung with pleural effusion or pneumothorax, this positioning usually entails placing the patient with the healthy lung down. This can lead to hypoventilation in the normal lung and potentially dangerous hypoxemia.

The patient should be monitored throughout the procedure. A minimum monitoring setting should include vital signs and oxygen saturation. Intravenous access should be in place, and equipment for cardiopulmonary resuscitation should be readily available. Local anesthesia is usually enough if administered in the right way; however, in cases of anxious patients with stable hemodynamic status, conscious anesthesia might be helpful.

Prophylactic antibiotic administration with chest tube placement is controversial. In the absence of trauma and with good sterile precautions, there is no need for prophylactic antibiotics with chest tube insertion.

After the patient is placed in the desired position, ultrasonography is used to confirm the radiological finding and to accurately choose the site of entry as mentioned above which should be marked with a water-soluble sterile marker. The procedure should be performed under strict sterile conditions. The skin over the area of insertion is prepared with either 10 % povidone-iodine solution or chlorhexidine and covered with sterile drapes.

Insertion Technique

The Seldinger Technique

SBCCs are most commonly inserted over a guidewire (*Seldinger technique*). Local anesthesia (e.g., 1–2 % lidocaine) is applied around the site of entry. Care should be taken to infiltrate skin, subcutaneous tissue, and the intercostal space that will be penetrated by the chest catheter (including the periosteum of the inferior rib and the parietal pleura) with generous amount of local anesthesia to minimize patient's pain and discomfort (Fig. 58.6). Ten to twenty

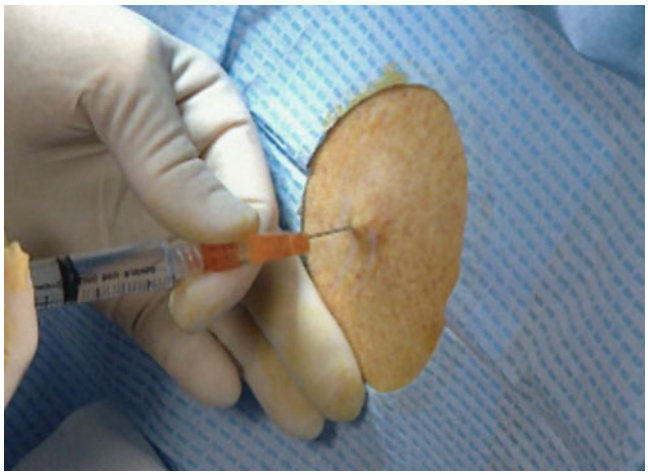

Fig. 58.6 Application of local anesthesia at the insertion site

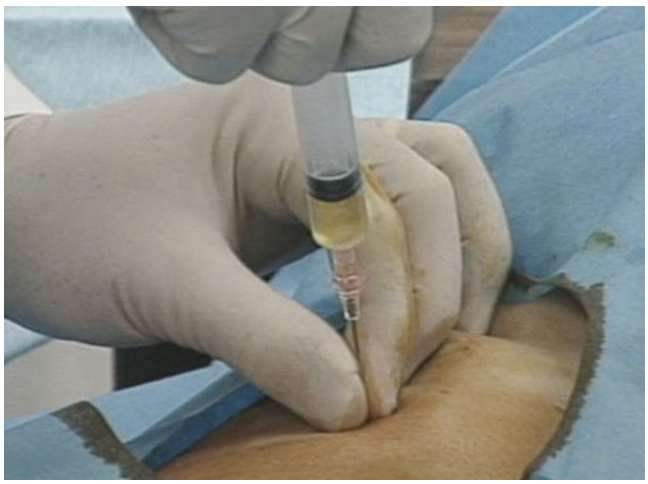

Fig. 58.7 The guiding needle is used to enter the pleural space

milliliter of lidocaine is usually needed for optimal analgesia. The intercostal neurovascular bundles (which run immediately below each rib) should be avoided by directing the route of entry at the upper edge of the inferior rib.

A small skin incision is made to insert an introducer needle (an 18-gauge single part needle) into the pleural space and aspirate for air or fluid to confirm the presence of sufficient pleural separation for the introduction of the chest catheter without the risk of parenchymal lung injury (Fig. 58.7). In case of pleural effusion, the fresh aspirated fluid should always be sent to the laboratory for appropriate analysis. The guidewire is then inserted through the introducer needle into the pleural space and directed to the desired place as mentioned above (apically for pneumothorax and inferiorly and posteriorly for pleural effusions). Then, the introducer needle is removed, and several dilators of gradually increasing size are serially passed over the guidewire to dilate the skin and subcutaneous tissue forming a tract to the chest catheter to pass. Dilators should be passed in a slow rotatory movement to avoid patient discomfort and accidental injury. After the last dilator (which is usually the size of the chest catheter) is removed, the chest catheter is placed over the guidewire to the pleural space, guidewire is removed, and the chest tube is sutured in place and connected to the pleural drainage system. The traditional teaching recommends limiting the initial aspirated volume to 1.5 L to avoid reexpansion pulmonary edema. However, this is controversial and will be discussed in more detail later in this chapter.

The Direct Trocar Technique

There are several commercially available kits for SBCC insertion using the direct trocar technique. They tend to be smaller in size and mostly used for pneumothorax. The advantage of such technique is that for emergency cases (tension pneumothorax), they can be inserted relatively faster than the Seldinger technique-operated catheters. When used for pneumothorax, local anesthesia is applied at the insertion site which is usually at the second intercostal space anteriorly, a small skin incision is made, and the catheter with the trocar inside is advanced into the pleural space until air or fluid is aspirated into the syringe. Then, the catheter is directed apically and advanced while holding the trocar in place. The trocar is then removed, and the catheter is sutured in place and connected to pleural drainage system.

Follow-Up Imaging

After the maximum comfortable volume of fluid has been drained, immediate follow-up imaging should be performed. This helps to confirm catheter position and evaluate for pneumothorax and lung entrapment. Chest radiograph is usually sufficient. However, in cases where complicated pleural space and loculated effusions are suspected (e.g., complicated parapneumonic effusion, hemothorax), CT may be superior. It can accurately define the pleural anatomy and assess the size and location of any residual fluid collections in relation to the catheter, which may need further intervention (e.g., additional SBCC insertion or intrapleural fibrinolytic therapy).

Pleural Drainage System

Pleural drainage systems typically consist of three parts: a collection chamber for pleural drainage, a suction source, and a mechanism to prevent air from entering the pleura during inspiration (Fig. 58.8). Modern devices vary in appearance, method of suction regulation, air preventing mechanisms, and volume of the fluid collection chambers. They are available as wet seal or dry seal systems (uses water seal or a one way valve to prevent air from entering the chest, respectively). In addition, the suction control can be either

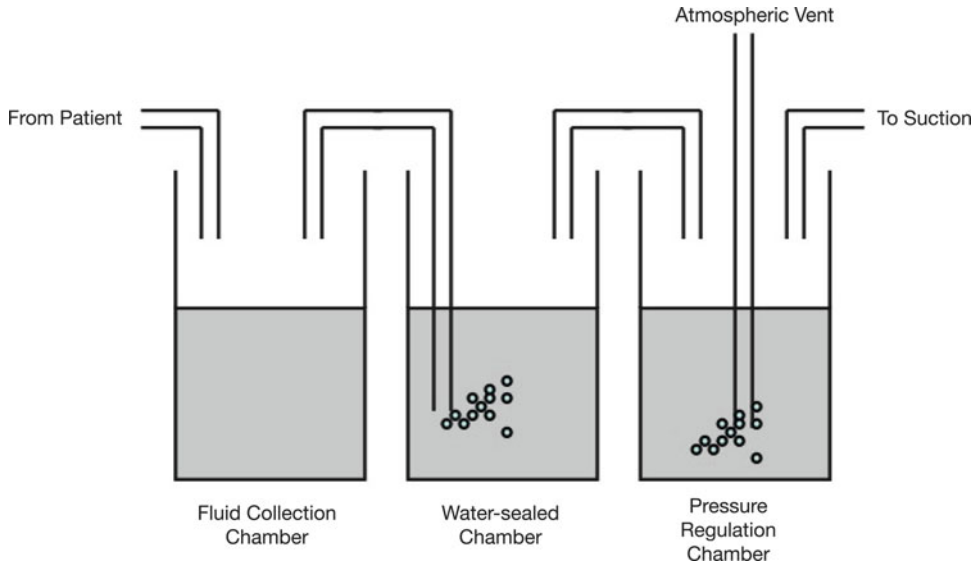

Fig. 58.8 Pleural drainage system

wet (where the level of water in the suction chamber controls the applied suction) or dry (uses a suction dial to control the applied suction).

Most of the traditional pleural drainage systems are water sealed with either dry or wet suction control. The typical system consists of three functional chambers. The first chamber on the right is the collection chamber, which is usually depicted with three subsections. Air or fluid from the chest tube accumulates in this chamber. The middle chamber is the water seal chamber that contains water at the bottom. Air from the patient enters this chamber below the water level and bubbles upward. The water seal prevents return of air to the patient. The last chamber on the left is the suction control chamber that is connected to wall suction, which is controlled with either water column (wet suction control) or a suction dial (dry suction control), as mentioned above. Suction pressures are typically between −10 and −40 mmHg.

Additional features of pleural drainage systems include a manual high-negativity vent, which prevents the application of excessive suction that may result in rapid evacuation of pneumothorax or pleural effusion. In addition, some devices come with a positive pressure relief valve that helps to prevent tension pneumothorax in cases where the line suction is accidentally disconnected or blocked.

Removal

The timing of SBCC removal depends on the original indication for its insertion and the clinical progress of the patient. In general, SBCC should be removed when the indication for their insertion is no longer present or the tube becomes nonfunctional. In cases of pneumothorax, SBCCs are removed when the lung is fully expanded with no evidence of air leak. In cases of pleural effusions, the SBCCs are removed when the lung is fully expanded and the daily fluid output is less 100–200 ml/day, although this is an arbitrary cutoff number.

Discontinuation of suction or clamping the chest tube prior to removal is a controversial issue and depends on the school of training. There is no evidence that either maneuver is beneficial. Nevertheless, 75 % of thoracic surgeons surveyed in one report favored chest tube clamping for 12–24 h prior to removal followed by a chest radiograph to detect small persistent air leak or fluid reaccumulation.

During chest tube removal, there is a risk of air entering the pleural space if the patient accidentally inhales during the procedure. This risk is much lower with SBCCs as the track left behind is smaller in size. Nevertheless, care should be taken to prevent this from happening. This can be avoided by asking the patient to inhale maximally and perform Valsalva maneuver or to remove the catheter during expiration while the intrapleural pressure is higher than the atmospheric pressure. In addition, using Vaseline gauze to seal the SBCC entry site during removal also helps to minimize air entry.

With SBCCs, suturing the site is usually unnecessary. Routine wound care and suture removal (in case one is used) at 3–5 days allows for optimum healing. A chest roentgenogram, 24 h following chest tube removal, for observation of residual air or fluid is recommended.

Complications

Data on complications associated with chest drains are mixed due to differences in insertion techniques, chest tube/catheter used, and studied population. In general, complications are infrequent when chest tubes are inserted under image guid-

ance and by expert operator. The reported incidence of chest drain complications ranges between 1 % and 3 %. Complications can be related to the insertion of the chest tube, pleural space aspiration, chest tube malposition, or draining system malfunction.

Complications Related to Chest Tube Insertion

During the insertion of a chest catheter, complications can occur at the level of the chest wall, pleural space, or thoracic structures. Pain is probably the most commonly encountered. It can arise from the skin, periosteum, and/or the parietal pleura which all receive rich sensory innervation. Pain can be minimized with the use of generous local anesthesia particularly directed to the above-mentioned structures. Anxiety and vasovagal attacks may also be encountered, and in selected patients, anxiolytics or sedative medications can be used to avoid such reactions.

The intercostal neurovascular bundle runs in a groove in the inferior surface of the ribs. Insertion of a chest catheter close to the superior rib may cause injury/avulsion of the intercostal vessels resulting in significant bleeding and/or local hematoma formation. To avoid such complication, coagulation parameters should be corrected before the procedure, and the catheter should be inserted in a "safe zone" about 50–70 % from the superior rib. This can prevent injury to the main neurovascular bundle (in the inferior surface of the superior rib) and collateral vessels (which lie on the superior surface of the inferior rib). Significant bleeding during chest tube insertion is reported to occur in less than 1 % of cases. Intercostal nerve injury either can be due to direct trauma and avulsion during the insertion of the catheter or can arise as a result of pressure effect on the nerve by the catheter.

Intrapleural adhesions and fibrous bands formation can occur with long-standing effusions, especially inflammatory or malignant. These adhesions when mature enough can be heavily vascularized and rich in friable blood vessels. During chest catheter insertion, those vascular structures can be injured resulting in intrapleural hemorrhage/hemothorax. When intrapleural adhesions are suspected or visualized during pre-procedure imaging, one should insure correction of coagulation profile prior to the procedure, and using the proper imaging technique, the insertion site should be chosen away from the adhesion.

The reported incidence of pneumothorax secondary to pleural aspiration is about 5 %. The incidence of pneumothorax seems to be less with image-guided techniques. Although it is usually blamed on accidental injury to the visceral pleura during the insertion of the chest catheter, other pathophysiological mechanisms play a part. Accidental entry of air may occur alongside the track of the chest catheter. This is more likely to occur in cases of trapped lung with high negative intrapleural pressures. Alternatively, during the expansion of a partially trapped lung, a transient pulmonary-pleural connection may occur due to visceral pleural shear stresses that allow air to enter the pleural space from the lung. Regardless of the underlying mechanisms, pneumothoraces secondary to pleural aspiration tend to be small, and aspiration of air is only required in less than 50 % cases. Subcutaneous emphysema may also occur when air ingress into the subcutaneous tissue usually from the pleural space. This can be avoided by minimizing the size of the parietal pleural entry site, regular drain flushes to prevent drain blockage, and use of large chest tubes in cases of large air leak.

Infection can be introduced during the insertion procedure but can occur as long as the chest catheter is in place. Infections can occur in the skin, subcutaneous tissue, or in the pleural space. The incidence of infective complication associated with chest drain insertion is in the range of 0.8–2.7 %. Strict sterile condition should be practiced in all cases of pleural procedures. When the sterile condition is suspected to be inadequate, especially in cases of emergency insertion, prophylactic antibiotics are advised to prevent future infection. This is supported by a recent meta-analysis of six studies of chest drains inserted in trauma victims, which supported the use of prophylactic antibiotics – there was an absolute risk reduction for pleural infection of 5.5–7.1 % and an overall infectious complication reduction of 12.1–13.4 %. The insertion site should be carefully inspected every time the dressing is changed looking for any signs of skin/subcutaneous tissue infection. Sudden unexplained increase in the chest catheter drainage should always raise the suspicion for pleural space infection. In such cases, pleural fluid should be immediately sent for analysis, and proper antimicrobial therapy should be initiated.

Complications Related to Pleural Space Aspiration

Some patients may experience cough and dyspnea during pleural fluid aspiration due to generation of high intrapleural negative pressure. This is particularly common in patients with trapped lung. Pleural pressure monitoring during fluid aspiration may help to prevent such complication.

Reexpansion pulmonary edema (RPE) is a well-recognized yet rare complication of rapid evacuation or the pleural space. The overall reported incidence of RPE is between 0 % and 29 %. The variability in the reported incidence is mainly due to the heterogeneity of the definition used. Clinically significant RPE seems to occur in less than 1 % of the cases. On the other hand, radiological evidence of RPE is a common finding after lung reexpansion and can be observed in up to 30 % of patients on CT scans. The clinical significance

of radiological RPE is unclear, and many patients in fact may experience improvement in their symptoms despite this radiological finding. The pathogenesis is poorly understood, and likely several factors are involved, including mechanical stress on a deformed pulmonary vasculature, anoxic injury related to oxygen-derived free radicals during reperfusion, and leukocytes sequestration with subsequent release of different inflammatory mediators. Several risk factors have been proposed for the development of RPE including the chronicity of the collapse, size of the pleural effusion/pneumothorax (as a surrogate for the size of the collapse), and the lung expansion technique regarding pleural pressure. The mortality rates associated with RPE are often quoted as high as 20 %. However, this number comes from a landmark review article more than two decades ago. More recent reports indicate that the mortality rates associated with this complication might be lower, possibly because of the advance in the critical care medicine and the early recognition and treatment of this complication.

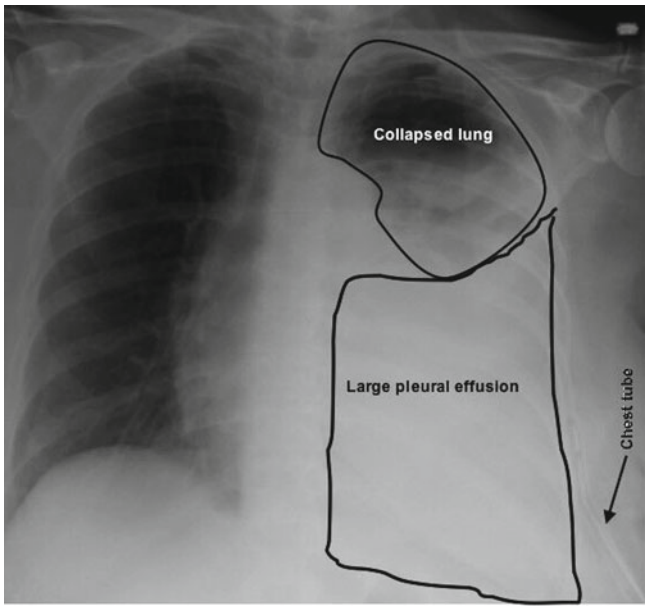

Fig. 58.9 Chest tube in the chest wall

Complications Related to Chest Drain Catheter Misplacement/Malposition

For an SBCC to function properly, both the tip and the draining ports have to be within the pleural space and in the proper location according to the underlying indication (apically for pneumothorax and inferiorly for pleural effusions). Despite proper insertion techniques, SBCC misplacement can occur. The most common scenario is improper tip placement in relation to the underlying pathology. If follow-up imaging shows good response, the SBCC can be left in place. Otherwise, SBCC should be manipulated or exchanged to insure proper drainage of the pleural space.

Extrathoracic placement (within the chest wall) of SBCC has been reported with an incidence ranging between 0.8 % and 2.6 %. The catheter can be totally or partially (only the draining port) within the chest wall (Fig. 58.9). This carries the risk of subcutaneous emphysema and infection. If only one of the proximal draining ports is within the chest wall, the SBCC can be advanced further into the pleural space under strict sterile condition. If most of the catheter is seen within the chest wall, or the sterile environment is suspected to be broken, the catheter should be immediately removed and replaced. Intrafissural placement of SBCC may occur with a reported incidence of 11.7 %. There is evidence that intrafissural drains may function as well as other normally placed drains. Drains that are functioning well despite lying within a fissure do not need replacement. However, if the catheter remains in this position for a long time, there is a hypothetical risk for erosion into the lung parenchyma resulting in bronchopleural fistula. Finally, intrapulmonary placement of SBCC can be catastrophic. The absence of air or fluid coming through the drainage system together with sudden hemoptysis is a clue to this complication.

Injury to thoracic structures has been rarely reported and includes misplacement of SBCC into the diaphragm, heart, sleep, liver, stomach, and abdomen. Other reported rare complications include chylothorax secondary to thoracic duct disruption. Contralateral pneumothorax can occur if the SBCC traverses the mediastinum and injures the contralateral visceral pleura. This kind of complications is less likely to occur with the use of image guidance that identifies risk factors for catheter misplacement such as raised diaphragm, loculated effusions, or hiatus hernia.

SBCC can also cause damage indirectly secondary to pressure effects, without actual perforation at time of insertion. Horner's syndrome, secondary to sympathetic chain damage, has been reported. Pressure on vascular structures can lead to cardiovascular compromise due to compression of the right ventricle or the aorta. Finally, delayed esophageal perforation has been reported due to erosion of chest tube into the esophagus. This type of complications, however, seems to be less likely to occur with the use of smaller catheters inserted under image guidance.

Complications Related to Drainage System Malfunction

Drainage system malfunction can arise due to problems in the SBCC itself, the connecting tubing, or the collecting chamber. The SBCC can be misplaced, malpositioned, kinked, or dislodged. With proper chest imaging and exam, these problems can be readily identified. SBCC can be

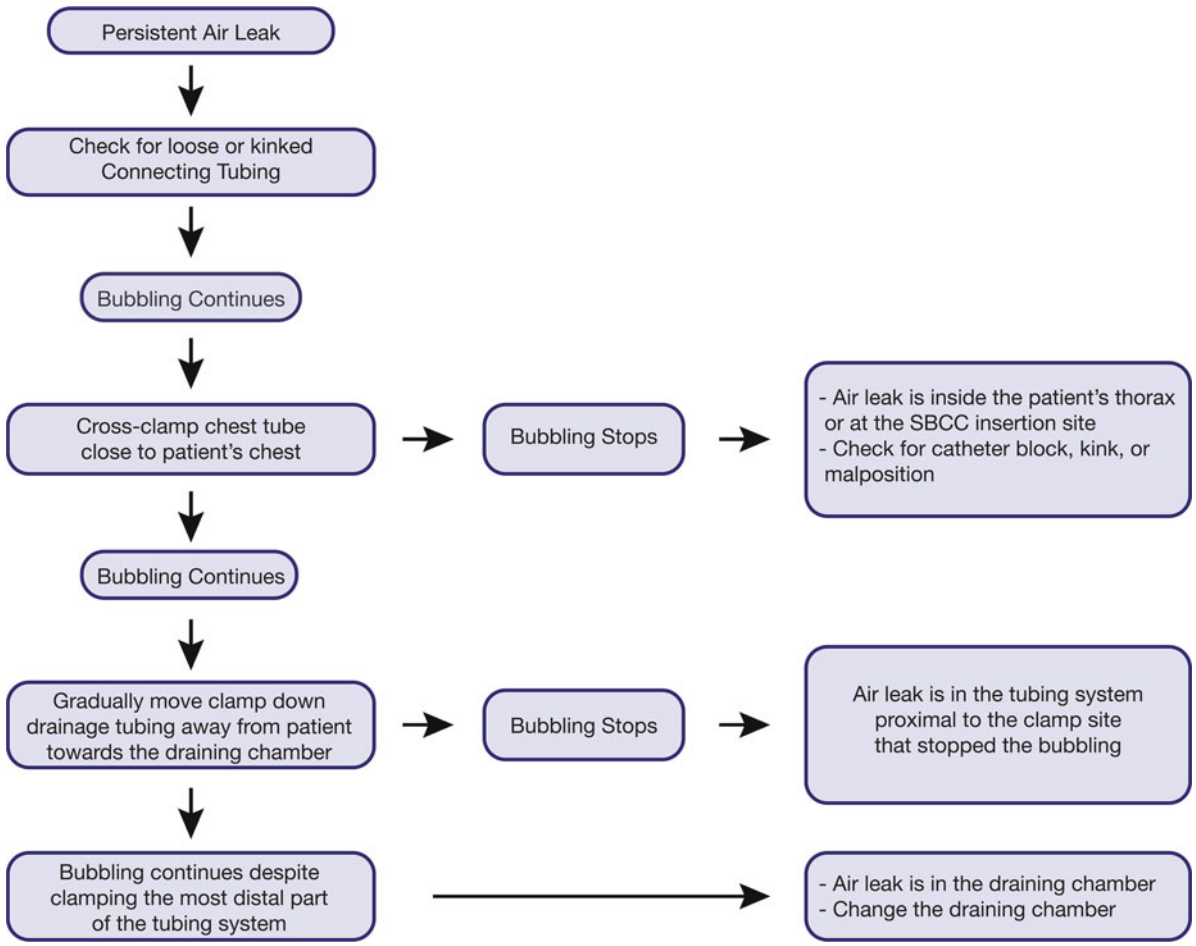

Fig. 58.10 Persistent air leak

blocked by fibrin debris. This is more likely to occur with smaller catheters and viscous effusions (empyema and hemothorax). This problem can be avoided by choosing a larger size catheter for viscous effusions and by routine frequent flushing of the drainage system. If the SBCC is blocked, flushing the system with normal saline may solve the problem. If the blockage persists, one may try local injection of fibrinolytic agent into the SBCC. If the SBCC is functioning properly, then the connecting tubing should be checked for kinking or disconnection.

In cases of pneumothorax, persistent continuous air leak can be encountered (Fig. 58.10). Before blaming the air leak on bronchopleural fistula, one should always check the drainage system for a leak. The first step is to clamp the SBCC as close to the chest wall as possible. If the leak stops, then one can be certain that the source of the leak is within the patient pleural space. In this case, the SBCC should be immediately unclamped to prevent the development of tension pneumothorax. If the air leak persists, then the site of the leak is distal to the chest wall in the connecting tubing or in the collecting chamber. In this case, the tubing system is clamped in a stepwise manner from the chest wall all the way to the collecting chamber to detect the site of the leak. If the air leak persists after clamping the most distal part of the tubing system, then the problem is in the collecting chamber, and it should be replaced.

Intrapleural Fibrinolytic Therapy

The use of intrapleural fibrinolytic therapy (IPFT) dates back to the 1940s. The rationale behind the use of IPFT is that the fibrinolytic agents can decrease the viscosity of thick gelatinous effusions (hemorrhagic effusions and complicated parapneumonic effusions), break down fibrinous septations and adhesions, and debride the pleura of fibrinous sheets, thus allowing reexpansion of the underlying lung. Initial attempts of IPFT were performed through non-image-guided placed large chest tubes. As the adhesions break and the lung expands, new septations usually form away from the drain-

ing chest tube and prevent complete evacuation of the pleural space. In the absence of image guidance, it is often difficult to precisely reposition large chest tubes into specific loculations or place multiple chest tubes into multiple loculations. As a result, the success rates of early IPFT series were not encouraging. With the recent advances in image-guided placement of SBCC, this limitation had been largely overcome, and IPFT has become more widely accepted.

In general, aggressive image-guided SBCC management is the most important factor in the successful drainage of viscous and loculated pleural effusions, and IPFT is a secondary adjunctive tool to facilitate drainage. Whenever the drainage is suboptimal with significant residual pleural fluid, cross-sectional imaging should be performed to evaluate the need for catheter repositioning or new catheter placement. IPFT rarely works when placed in a malpositioned catheter away from the pleural collection.

Summary

Image-guided SBCC placement has been evolved over the last decade as a safe and effective treatment option for pleural space evacuation. It has the advantage of less patient discomfort and invasiveness, together with the ease and speed of their placement. Their outcomes are comparable to large-bore chest tubes in most cases. Proper training is mandatory to insure proper SBCC placement and to prevent complications.

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Medical Thoracoscopy/Pleuroscopy

59

Robert Loddenkemper

Introduction

Thoracoscopy, introduced more than 100 years ago, is – after bronchoscopy – the second most important endoscopic technique in respiratory medicine. In the past, the vast majority of respiratory specialists performed only flexible bronchoscopy, thoracentesis, and chest-tube placement. A growing number now perform medical thoracoscopy/pleuroscopy (MT/P) as well.

MT/P is an invasive technique that should be used to obtain a diagnosis only when other, simpler methods are nondiagnostic (mainly in case of pleural exudates). But, in addition to its several diagnostic applications, it offers certain therapeutic possibilities, in particular talc poudrage, to achieve pleurodesis in case of recurrent pleural effusion or pneumothorax.

However, MT/P is less invasive than surgical thoracoscopy (VATS) because it is performed under local anesthesia and conscious sedation, most commonly through a single entry. It is also less expensive because it can be performed in an endoscopy suite, using a nondisposable rigid or semirigid endoscope, and usually does not require an anesthesiologist (Table 59.1).

As with all technical procedures requiring special skills, there is a learning curve before full competence is achieved. Appropriate learning is therefore mandatory. The technique is actually very similar to chest-tube insertion by means of a trocar, the difference being that the thoracoscope/pleuroscope is introduced before insertion of the chest tube. Thus, the whole pleural cavity can be visualized, and biopsies can be taken from all areas of the pleural cavity, including the chest wall, diaphragm, lung, and even mediastinum. In general, MT/P is easier to learn than flexible bronchoscopy if sufficient expertise in thoracentesis and chest-tube placement has already been gained. When indicated, talc poudrage can be performed prior to chest-tube insertion, allowing a very homogeneous distribution of talc on the visceral and parietal pleura. Today, this is the gold standard for nonsurgical pleurodesis.

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Historical Development

Probably the first thoracoscopy was performed as early as 1866 by Francis-Richard Cruise in Ireland. This was brought to light only recently.

However, Hans-Christian Jacobaeus in Sweden has to be regarded as the father of thoracoscopy since he introduced the technique together with laparoscopy in 1910 and made it known worldwide by many publications and lectures. Primarily, in his pioneer paper (published in German in the "Münchner Medizinische Wochenschrift," one of the leading journals at that time), Jacobaeus used the method for diagnosis in tuberculous pleural effusions. He defined three main prerequisites which are still valid today: (1) the possibility to introduce a trocar into the relevant cavity without lacerating the inner organs and without causing too much pain, (2) introduction of a transparent medium into the cavity (Jacobaeus used filtered air for this purpose), and (3) an endoscope of such small dimensions that it can be introduced through the trocar.

But already in 1913, Jacobaeus applied the technique also for therapeutic purposes. He used it for cauterization of adhesions between the parietal and visceral pleura which prevented a complete artificial pneumothorax required for the collapse therapy of pulmonary tuberculosis. The technique, with two different points of entry under local anesthesia, called "Jacobaeus operation," became very popular in the pre-antibiotic era for treatment of tuberculosis and was applied during the ensuing 40 years on a worldwide scale almost exclusively for this purpose.

Only with the advent of antibiotic treatment of tuberculosis in the 1950s, the therapeutic use of thoracoscopy in the

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treatment of tuberculosis came to an end. At the same time, other diseases became more important to the chest physician, and, consequently, a generation of physicians already familiar with the therapeutic application began to use thoracoscopy on a much broader basis for diagnostic evaluation of many pulmonary diseases, mainly in Europe. Today, MT/P is considered as an integral part of interventional pulmonology.

At the beginning of the 1990s, following the experience of abdominal surgeons with minimally invasive surgery, thoracic surgeons introduced these techniques for "surgical thoracoscopy" or "video-assisted thoracic surgery (VATS)."

To clarify the difference between the two methods, the term "medical thoracoscopy" was introduced. However, because the term "thoracoscopy" is used for both the medical and surgical procedures, a degree of uncertainty has arisen, which may lead to unnecessary surgical interventions for what are, in fact, medical indications (Table 59.2). To avoid confusion in the future, it has been suggested that the old term "pleuroscopy," as used already in 1923, should be favored over "medical thoracoscopy," both terms are used today in an interchangeable way.

In several European countries, MT/P has already been part of the training program in respiratory medicine for many years, and it is now becoming more popular in the United States, where according to the national survey in 1994, MT/P was applied frequently by 5 % of all pulmonary physicians. Although newer data are not available, the interest in the technique seems to be increasing; however, training is lacking. In an American College of Chest Physicians (ACCP) survey of US pulmonary/critical care fellowship programs in 2002/2003, only 12 % of the directors stated that MT/P was offered in their programs. In the United Kingdom, where medical thoracoscopy was underutilized compared with the rest of Europe, there is also growing interest. Meanwhile, the technique has been introduced successfully in Australia, as in many Asian, South American, and some African countries.

Table 59.1 Main differences between medical thoracoscopy/pleuroscopy versus surgical thoracoscopy/video-assisted thoracic surgery (VATS)

Feature	Medical thoracoscopy/ pleuroscopy	VATS
Purpose	Diagnosis	Minimally invasive thoracic surgery
	Pleurodesis	
Location	Endoscopy suite	Operating room
	Operating room	
Anesthesia	Local with moderate sedation	Single-lung ventilation
Technique	Single puncture	Multiple punctures
	Double puncture	
Instruments	Nondisposable	Disposable
	Simple	Complex

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Techniques

The modern principles and techniques of MT/P using rigid instrumentation were developed in continental Europe during the second half of the last century. These principles remain valid for use of the newer generation of semirigid (semiflexible) pleuroscopes, too.

Table 59.2 Indications for medical thoracoscopy/pleuroscopy (MT/P) versus surgical thoracoscopy (VATS) versus the middle column where both methods can be used

MT/P	MT/PorVATS	VATS
Pleural effusions	Spontaneous pneumothorax	Lung procedures
Pleural effusions of unknown etiology	Staging	Lung biopsy
Staging of lung cancer	Pleurodesis by talc poudrage	Lobectomy
Staging of diffuse malignant mesothelioma	Empyema (stage I/II)	Pneumonectomy
Pleurodesis by talc poudrage or any other agent	Drainage	Decortication
	Diffuse pulmonary diseases	Lung volume reduction surgery
	Localized lesions	Pleura procedures
	Chest wall, diaphragm	Pleurectomy (pneumothorax)
	Sympathectomy, splanchnicectomy	Drainage/decortication (empyema stage III)
		Esophageal procedures
		Excision of cyst, benign tumors, esophagectomy, anti-reflux procedures, mediastinal procedures
		Resection of mediastinal mass
		Thoracic duct ligation
		Pericardial window
		Sympathectomy

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Pulmonologists nowadays use two different techniques for performance of diagnostic and therapeutic thoracoscopy. One method recommends a single entry site, the use of a usually 9-mm rigid thoracoscope (or of a semirigid/semiflexible 7-mm pleuroscope) with a working channel for accessory instruments and optical biopsy forceps, and is most often performed under local anesthesia. The other method requires two entry sites – one for a 7-mm trocar for the examination telescope and the other for a 5-mm trocar for accessory instruments, including the biopsy forceps – and is usually performed with conscious sedation or general anesthesia. As with all technical procedures, there is a learning curve before full competence is achieved. Since the technique is actually very similar to chest-tube insertion by means of a trocar, sufficient expertise in thoracentesis and chest-tube placement is mandatory. The difference to the latter is only that with MT/P, the pleural cavity can be visualized and biopsies can be taken from all areas of the pleural cavity, including the chest wall, diaphragm, mediastinum, and lung, under direct visual control. When indicated, talc poudrage can be performed additionally.

For most indications, MT/P will start as a single-port, single-instrument rigid procedure, as first described by Jacobaeus for diagnostic purposes. However, with the introduction of the semirigid/semiflexible pleuroscope, which is similar in design, accessory equipment, and handling to the flexible bronchoscope, MT/P can now be performed in a fashion analogous to flexible bronchoscopy. Thus, this technique is now increasingly used by pulmonologists who are experienced with video-controlled flexible bronchoscopy.

Equipment

Since the first detailed description by Jacobaeus in 1910, rigid endoscopic instruments such as stainless-steel trocars and endoscopes have been pivotal in the performance of thoracoscopy (and VATS). With the introduction of the semirigid/semiflexible pleuroscope, similar in design and handling to the flexible bronchoscope, pleuroscopy is now frequently performed with this technique. An additional advantage is that parts of the bronchoscopy equipment (e.g., the light source, processor, and monitor) can be used, reducing the acquisition costs.

The equipment requirements include trocar, thoracoscope/pleuroscope, biopsy forceps, unipolar coagulation forceps, light sources, video system, aspiration system, talc, chest tubes, and drainage systems. The usual diameter of the rigid thoracoscope is 7–9 mm, that of the semirigid pleuroscope 7 mm. For the rigid technique, optical devices exist with various fields of view (0, 30, and 90 °); trocars are also available with diameters of 5 and 3.75 mm for performing thoracoscopy in children. The trocar consists of an obturator and cannula with a blunt conical tip, adjacent to which there is a small hole connected to the trocar lumen, open to the exterior, so that penetration into the pleural cavity is signaled. Unlike the instruments for laparoscopy, this trocar does not have to be airtight. Air should be allowed to enter and leave the thoracic cavity freely. Examination will be limited by pain if the diameter of the trocar is larger than 10 mm.

Figure 59.1 shows a selection of rigid thoracoscopy instruments (Fig. 59.1). Besides the biopsy forceps, needle biopsy, and suction catheter, the working channel also accommodates electrocautery. A bajonet optical system with an instrumentation channel and the appropriate instruments may facilitate direct fluid suction, electrocautery, or direct insufflation of talc. A Xenon light source satisfies the requirements for high-quality visual exploration and video documentation. The inspection of the pleural space can be performed either directly through the telescope or indirectly by video (Figs. 59.2 and 59.3). Today, most – if not all – centers use video systems.

Rigid mini-thoracoscopes were recently introduced, but they have the disadvantage that a second point of entry is necessary for biopsy purposes, and insertion of a large drainage catheter through the same channel post-thoracoscopy is impossible. The semirigid/semiflexible pleuroscope has been developed by the Japanese company Olympus in conjunction with pulmonologists for a single-puncture technique. The pleuroscope consists of a handle that is similar to the standard flexible bronchoscope and a shaft that measures 7 mm in outer diameter and 27 cm in length (Fig. 59.4a–c). The shaft is made up of two sections: a 22-cm proximal rigid portion and a 5-cm flexible distal end. The flexible tip is movable by a lever on the handle, which allows a two-way angulation capability of 160 ° up and 130 ° down. It also has a 2.8-mm working channel that accommodates biopsy forceps, needles, and other accessories and is compatible with various electrosurgical and laser procedures (Fig. 59.5). The instrument is used with a single-port technique with a disposable 8-mm inner diameter flexible trocar (Figs. 59.6 and 59.7). The new LTF 160 model allows autoclaving, thereby obviating important questions and issues related to sepsis (Fig. 59.8a, b). The other notable advantage of the semirigid pleuroscope over rigid instruments is that it interfaces easily with existing processors and light sources made by the manufacturer for flexible bronchoscopy or gastrointestinal endoscopes, which are available in most endoscopy units without additional costs (Fig. 59.9).

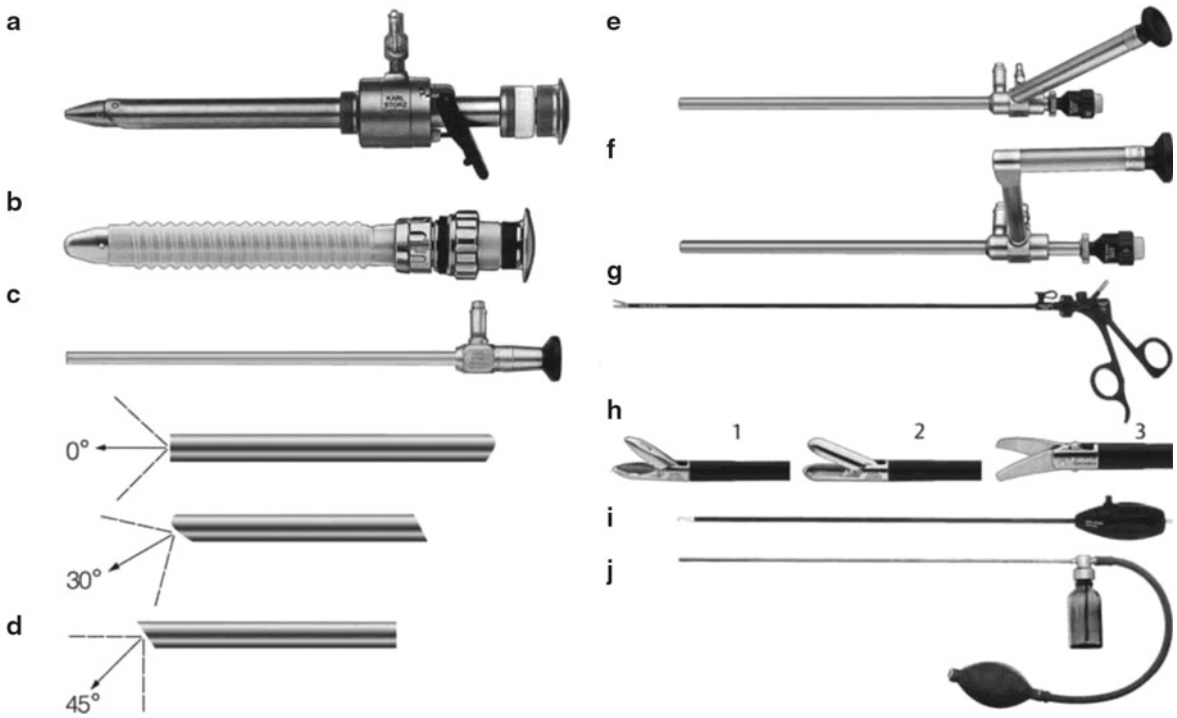

Fig. 59.1 Selection of instruments for rigid medical thoracoscopy. (**a**) Trocar with multifunctional valve with insufflation stopcock, 11 mm, autoclavable. (**b**) Trocar with silicone leaflet valve, 11 mm, autoclavable. (**c**) Telescope, particularly suited for single-incision thoracoscopy, here with light shaft for photography, diameter 10 mm, length 31 cm, trocar size 11 mm. (**d**) Various fields of view. (*1*) Straightforward telescope 0 °, diameter 10 mm, length 31 cm, autoclavable; (*2*) Forward-oblique telescope 30 °, diameter 10 mm, length 31 cm, autoclavable; (*3*) Telescope 45 °, diameter 10 mm, length 31 cm, autoclavable. (**e**) Straightforward telescope 0 ° with angled eyepiece, diameter 10 mm, working length 27 cm, with instrument channel 6 mm, trocar size 11 mm, single puncture. (**f**) Straight-forward telescope 0 °, with parallel eyepiece (bayonet optic), diameter 10 mm, working length 27 cm, with instrument channel 6 mm, trocar size 11 mm, single puncture. (**g**) Dissecting and biopsy forceps, rotational, that can be dismantled, with connector pin for unipolar coagulation, 5 mm. (**h**) Single-action jaws: (*1*) dissecting and biopsy forceps: (*2*) biopsy forceps; (*3*) scissors. (**i**) Dissecting electrodes, with connector pin for unipolar coagulaton, L-shaped, size 5 mm, working length 43 cm. (**j**) Powder blower, with rubber bulb, size 5 mm, working length 42 cm (Reprinted with kind permission from Karl Storz GmbH & Co. KG, Tuttlingen, Germany)

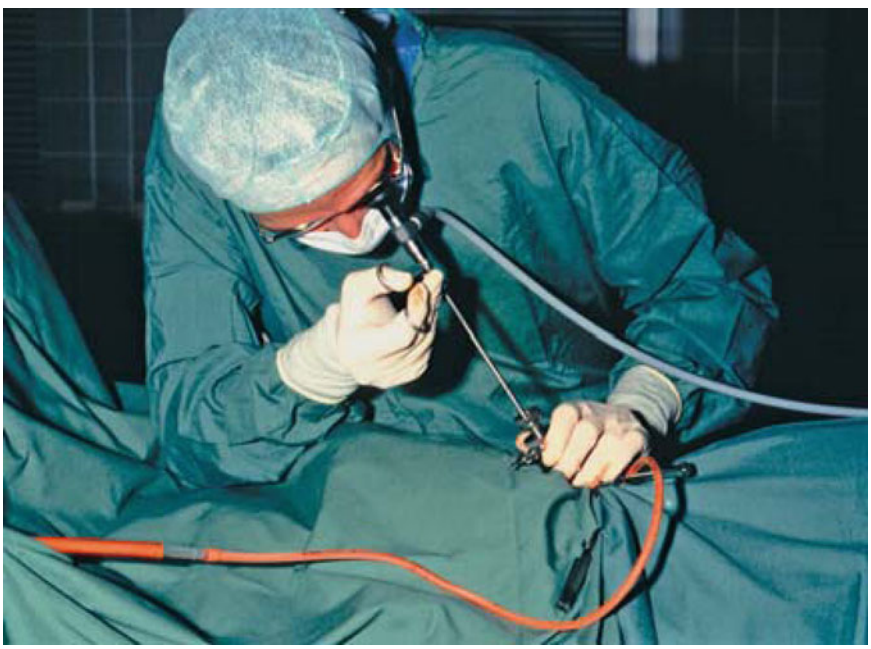

Fig. 59.2 Direct inspection through the rigid thoracoscope (while taking a biopsy) (Reprinted with permission from Loddenkemper R, Mathur PN, Noppen M, Lee P. Medical thoracoscopy/pleuroscopy: manual and atlas. Stuttgart: Thieme; 2010)

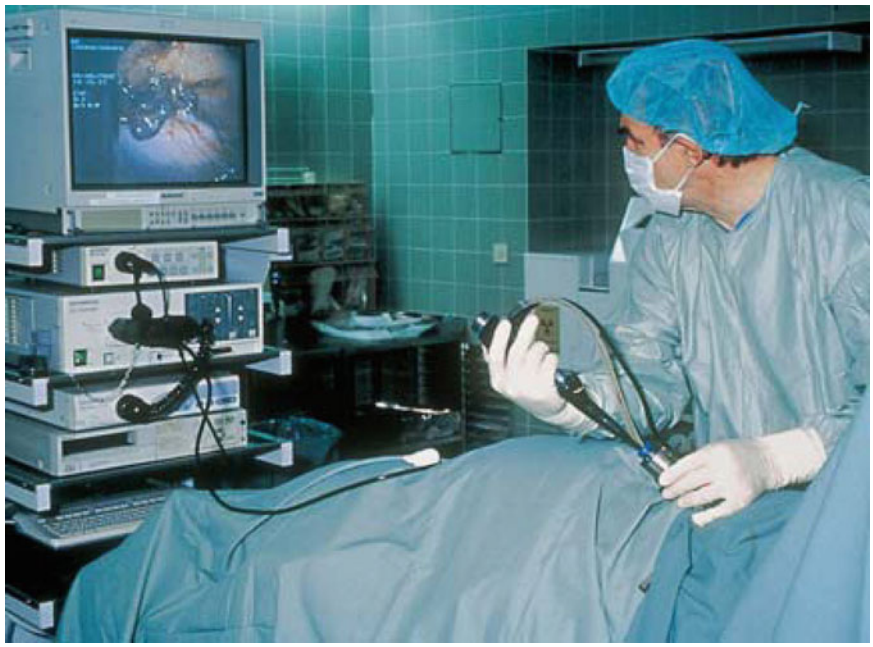

Fig. 59.3 Indirect, video-controlled inspection of the pleural cavity through the semiflexible pleuroscope (Reprinted with permission from Loddenkemper R, Mathur PN, Noppen M, Lee P. Medical thoracoscopy/pleuroscopy: manual and atlas. Stuttgart: Thieme; 2010)

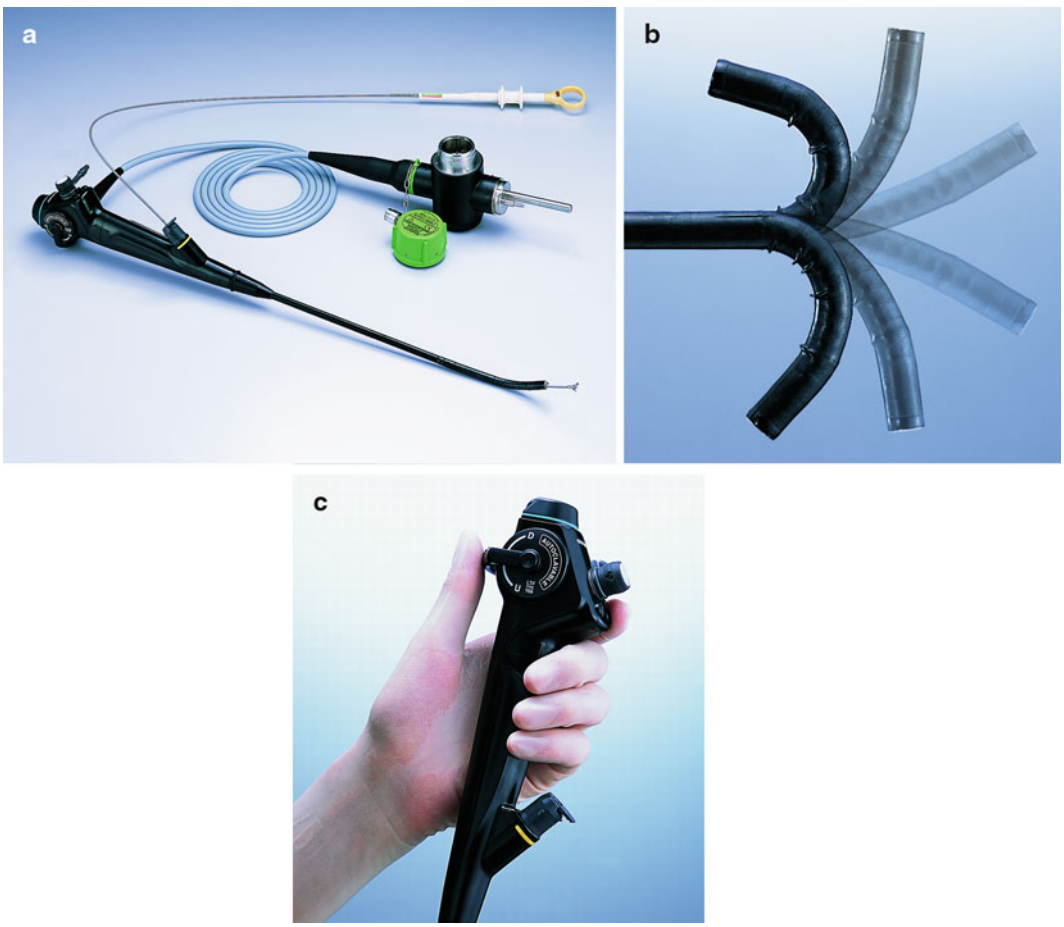

Fig. 59.4 (**a**) The semirigid (semiflexible) pleuroscope (Olympus Corporation). Control section allows handling as with the flexible bronchoscope. (**b**) Angulation capability 160 ° upward/130 ° downward. (**c**) Diameter of the pleuroscope 7-mm, with a 2.8-mm diameter of the working channel (Reprinted with kind permission from Olympus Corporation)

Fig. 59.5 Additional accessories for electrosurgical and laser procedures that can be introduced through the semirigid (semiflexible) pleuroscope. (**a**) Spray catheter. (**b**) (*left to right*) Coagulation electrode, hot biopsy forceps, electrosurgical knife ((**a**) and (**b**) reprinted with kind permission from Olympus Corporation)

Fig. 59.6 Rigid trocar and cannula with valve for the semiflexible pleuroscope (Olympus). Outer diameter 10 mm, inner diameter 8 mm

Comparison of the Rigid and Semirigid Technique

Advantages of the rigid thoracoscopic instruments are, besides larger biopsy sizes, that the rigid forceps allows taking of biopsies from very dense lesions, too. The rigid instruments are also more suitable when more elaborate procedures are indicated or when it is necessary to control hemorrhage after biopsy. Rigid instruments are less expensive, more robust, have a longer endurance, and may need maintenance and repair less often (Tables 59.3 and 59.4).

The advantage of the semirigid pleuroscope is that it has the "look and feel" of a flexible bronchoscope, and thus may "lower the threshold" for MT/P for the pulmonologist. It may also be helpful psychologically in overcoming fear of using the rigid (and therefore often regarded as more dangerous) instruments. In addition, it helps maintain a clear optical

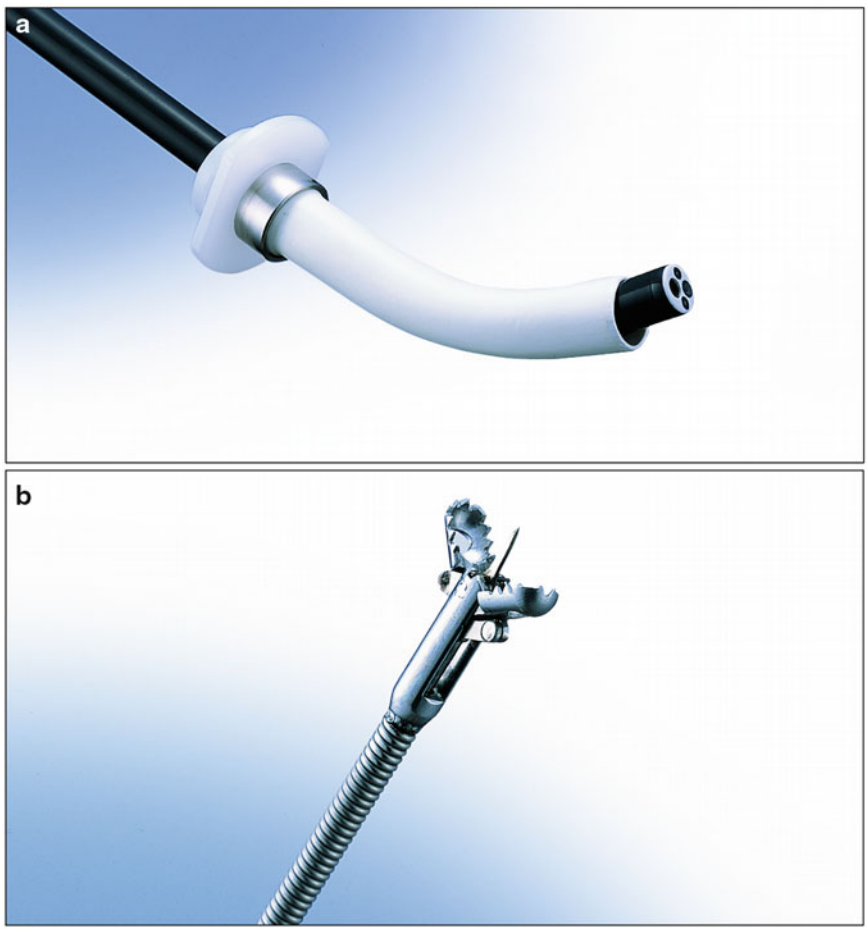

Fig. 59.7 (**a**) Pleuroscope with the flexible forceps, introduced through the trocar shaft. (**b**) Swing-jaw needle forceps (alligator jaw type) (Reprinted with kind permission from Olympus Corporation)

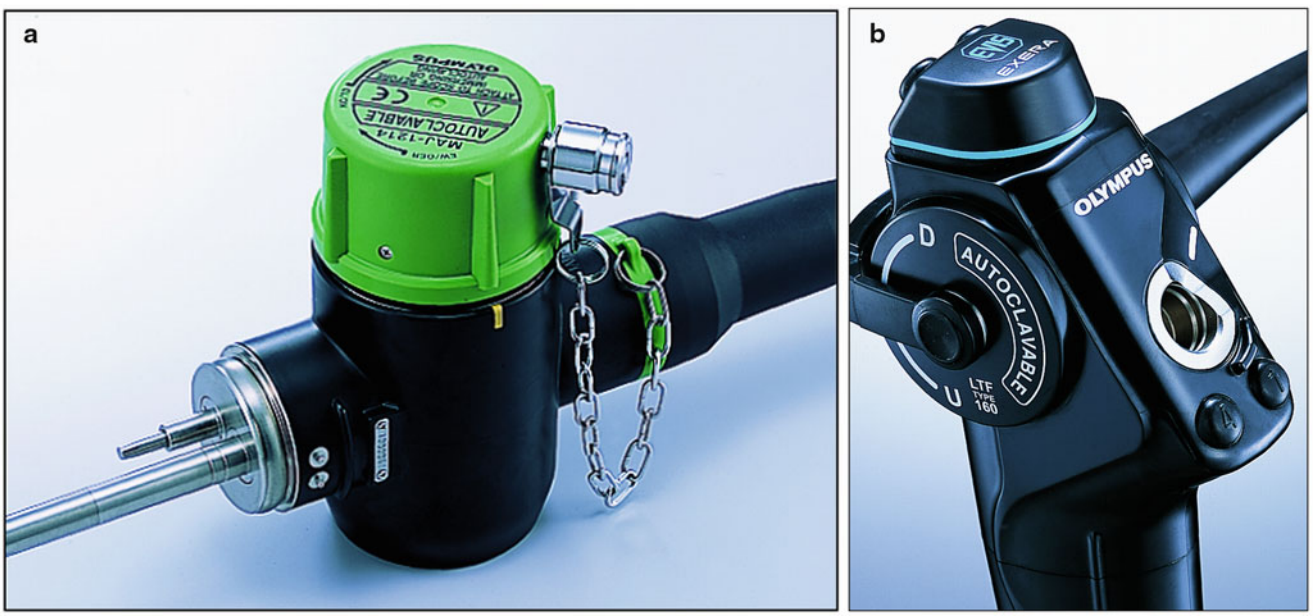

Fig. 59.8 (**a**) A dedicated, green waterproof cap protects the electrical connections of the LTF 160 pleuroscope during autoclaving. (**b**) Waterproof control section (Reprinted with kind permission from Olympus Corporation)

Fig. 59.9 Light source, processor, and monitor used with the bronchovideoscope (Reprinted with kind permission from Olympus Corporation)

field by allowing concurrent suctioning, which is analogous to the suction techniques used during flexible bronchoscopy, and it may allow one to overcome a limited view by maneuvering its flexible tip in different directions and around adhesions. Its flexible tip facilitates the homogeneous insufflation of talc (via a catheter), introduced through the working channel, into all areas of the parietal and visceral pleura.

The ideal is certainly the combination of both techniques, in which rigid MT can be complemented by the semiflexible pleuroscope in the above-mentioned advantageous situations, which is comparable to the combined use of rigid and flexible bronchoscopy in complex therapeutic endobronchial indications.

MT/P can be performed in the operating room or in an environment dedicated to invasive procedures such as a clean endoscopy room. The personnel required to perform endoscopy include an endoscopy nurse (or an endoscopy assistant) to assist with the instrumentation, an additional assistant outside the sterile field to bring necessary equipment, and the physician performing MT/P. Ideally, an additional person sits at the patient's head and monitors his or her overall condition. In an emergency, MT/P can be performed with only a physician and a nurse, but this is less efficient and prolongs the procedure.

Table 59.3 Advantages of rigid medical thoracoscopy

Trocar with multifunctional valve
Larger biopsy specimens
Biopsies from dense lesions easier to take
More suitable for elaborate procedures, extensive adhesiolysis, lung biopsies, sympathicolysis, etc.
Less expensive, more robust, and less maintenance and repair cost

Table 59.4 Advantages of semiflexible pleuroscopy

"Look and feel" of a flexible bronchoscope (lower threshold for the chest physician)
Interfaces easily with existing processors and light sources for flexible bronchoscopy/GI endoscopy (without additional cost)
Allows better view by maneuvering the flexible tip into different directions and around adhesions
Flexible tip facilitates homogeneous insufflation of talc (talc poudrage)

The procedure suite should be equipped with monopolar and, if possible, bipolar electrocoagulation as well as equipment for resuscitation, assisted ventilation, electrocardiography, and blood pressure monitoring and a defibrillator, as well as an oxygen source and a pulse oximetry system.

Knowledge and Skills Required for MT/P

To learn MT/P, the pulmonologist needs to know the exact topographical anatomy of the thorax, the pathophysiology and pathology of respiratory diseases, their diagnostic approach and their management options, in particular of pleural diseases, as well as the clinical prerequisites, the contraindications, and the potential complications of the technique. He or she must also know the details of the technique of MT/P including all instruments used, the different options of access to the pleural space, the technique of coagulation, and so on, as outlined later. In addition, he or she should already have adopted certain skills in the diagnosis and treatment of respiratory diseases, particularly pleural diseases.

The learner should already have acquired skills in the following: application of the above knowledge, diagnostic and therapeutic thoracentesis, performance of local anesthesia, closed needle biopsy of the pleura, familiarity with chest tubes and pleural drainage, closed chest-tube insertion, pleurodesis techniques, flexible bronchoscopy, rigid bronchoscopy (optional), use of either the semirigid pleuroscope or the rigid thoracoscope (or both), use of biopsy forceps and other instruments, use of coagulation systems, use of the talc atomizer/talc spray, use of video-endoscopic equipment, ultrasonography, and/or fluoroscopy (optional).

Technical skills are best learned under the direct supervision of an experienced thoracoscopist. Because manual dexterity, confidence, and expertise may vary from one physician

to another, it is difficult to specify a minimum number of procedures necessary to obtain the skill or to maintain competence. It is unlikely that any specific number of procedures will guarantee competence. However, a minimum number of 20 procedures are desirable to achieve sufficient familiarity with the instrumentation and interpretation of normal and pathological thoracoscopic findings. Procedural competence can probably be maintained if about 10–20 thoracoscopies are performed yearly.

Adequate training in both the cognitive and technical aspects of MT/P is essential. This is unlikely to be provided by a single 2-day course. Training courses should be encouraged and may be extremely beneficial if they follow certain guidelines and include didactic lectures as well as laboratory sessions. By attending hands-on training seminars, lectures, and symposia, physicians can learn basic concepts and acquire a greater understanding of the appropriate indications, risks, benefits, and limitations of MT/P. These sessions should allow physicians to achieve familiarity and comfort with basic thoracoscopic/pleuroscopic techniques and instrumentation. Physicians should be encouraged to work with a mentor within their community until the necessary criteria are met for MT/P privileges within their own institutions. This form of a mini-fellowship may be ideal for training physicians in procedures not learned during formal subspecialty training. A good opportunity to learn inspection of the pleural space and its pathological situation is given by observation of procedures on a video screen or live transmission into a bigger group. Also, manuals describing in detail the technique including the demonstration of endoscopic photos will be helpful. As with all technical procedures, there is a learning curve before full competence in MT/P is achieved, although it is easier to learn than flexible bronchoscopy. The recommendation for beginners is to start with easy situations such as a large pleural effusion or a pneumothorax when placement of a chest tube is indicated.

Point of Entry

The point of entry is generally near the mid-axillary line, within the axillary triangle. The axillary triangle has no large muscle obstructing passage of the instruments: it is bordered anteriorly by the lower edge of the pectoralis major muscle, posteriorly by the anterior edge of the latissimus dorsi muscle, and inferiorly at the level of the diaphragmatic insertions. Its apex reaches the second intercostal space. The final location of the insertion port will be determined by the indication: for pleural effusions most commonly in the fifth, sixth, or seventh intercostal space. The last two spaces are especially preferred when metastatic tumor and diffuse malignant mesothelioma are suspected to reach the most common sites of these malignancies. This provides an excellent view of both the diaphragm and the costovertebral gutter where malignant lesions, if present, will usually be reachable.

In case of spontaneous pneumothorax, the entry port will be located at the third or fourth intercostal space to allow thorough inspection of the lung apex and because the leak, if present, is usually in the upper lobe.

In different indications, other points of entry are used depending on the clinical setting and/or the chest radiography/CT or ultrasound results.

Access to the Pleural Space

Since it is impossible to perform the procedure if the pleural space is completely obliterated, the lack of a sufficiently large pleural space is an absolute contraindication. Thus, the most important prerequisite for MT/P is a freely accessible pleural space that allows introduction of the trocar and thoracoscope/pleuroscope without injury to the lung or other organs (it should be recalled that the diaphragm lies in a much higher position in the supine than in the upright patient). Before insertion of the thoracoscope/pleuroscope, some important points have to be considered, thus providing a safe entry to the pleural space: a pleural symphysis can be suspected from the patient's history (previous pleurisy or thoracic surgery) or/and from imaging (radiography, CT, MRI, ultrasound, and/or fluoroscopy). A partial pneumothorax of at least 100–200 ml should be present or induced to permit introduction of instruments without risk. The simplest access is available in case of a preexisting complete pneumothorax (Table 59.5). If the preexisting pneumothorax is only partial, due to adhesions, these should be localized by the imaging techniques to avoid introduction of the trocar in the area of the adhesions. In the presence of a large pleural effusion, the trocar can also be introduced directly without producing a pneumothorax (if fluid is readily aspirated as the pleural space is entered), although this may carry a somewhat greater risk of injury in case of unsuspected adhesions. In the presence of a smaller pleural effusion, a needle puncture should be performed at the level of the greatest opacification dullness or, ideally, under sonographic or fluoroscopic guidance. When pleural fluid is aspirated, the syringe is removed from the needle and air will enter into the pleural space either spontaneously or when asking the patient to take a few deep breaths. The entry of air causes the lung to collapse away from the chest wall and creates a pleural space for safe trocar insertion.

If it is difficult to aspirate pleural fluid, the pneumothorax can be induced with special pneumothorax needles, under pressure control, ideally with a manometer or a pneumothorax apparatus. In case of difficulties in creating a pneumothorax because of adhesions, the blunt dissection technique is

Table 59.5 Different situations of access to the pleural space

Preexisting complete pneumothorax
In case of a partial pneumothorax, at least 100–200 ml should be present
In the presence of a large pleural effusion, the trocar can be introduced directly (if fluid is readily aspirated as the pleural space is entered)
In the presence of a small pleural effusion, a needle puncture should be performed under sonographic or fluoroscopic guidance. When pleural fluid is aspirated, air can be introduced through the needle into the pleural space either spontaneously or by means of a syringe
If it is difficult to aspirate pleural fluid, the pneumothorax can be induced with special pneumothorax needles under pressure control, ideally with a manometer or a pneumothorax apparatus
In case of difficulties in creating a pneumothorax because of adhesions, a blunt dissection technique using a (Kelly) forceps and a finger can be applied
If the pleural space is completely obliterated, MT/P is contraindicated

For more information, see Loddenkemper et al. Medical thoracoscopy/pleuroscopy: manual and atlas. Stuttgart: Thieme; 2010

recommended. This usually involves gentle dissection of the pleural adhesions with the finger to verify the existence of a free pleural space before advancing the instrument into the pleural space. If unbreakable, dense adhesions are felt, another point of entry should be selected (or the whole procedure should be stopped and a closed needle biopsy or a surgical approach be substituted).

If neither effusion nor pneumothorax is present, for example, in MT/P for biopsies in diffuse lung disease, an artificial pneumothorax must be created either by the blunt dissection technique using the finger or by the technique of pneumothorax induction as introduced by Forlanini as early as 1888.

Anesthesia for MT/P

The anesthesia technique varies: MT/P is commonly performed under local anesthesia with moderate sedation, which is quite well tolerated by patients. The term "conscious sedation" is widely used in the literature and refers to patients who remain awake or arousable during the procedure while given mild anxiolytics and pain medications. With conscious sedation, an anesthesiologist is not needed, which saves costs.

MT/P, in contrast to VATS, does not normally require tracheal intubation with either a single- or double-lumen tube. However, general anesthesia may be preferable in some special indications, such as idiosyncratic or allergic sensitivities to local anesthetics, in very anxious or uncooperative patients including children, or for advanced procedures such as sympathectomy and others.

An excellent alternative today is intravenously administered propofol (with or without premedication), which provides sedation similarly to midazolam but with a faster onset of action and a more rapid recovery.

MT/P may be a painful and unpleasant procedure: unpleasant because of the position of the patient, instrument manipulations, and vagus-mediated reflexes and painful during certain well-defined periods of MT/P as at the beginning of local anesthesia; during the examination, that is, by the pressure of the endoscope acting as a lever on the ribs; during removal of adhesions by coagulation, at biopsies of the chest-wall pleura; and, in particular, in the minutes following insufflation of talc.

In general, the pleura is more algesic in younger than in older patients and in patients with a normal surface of the parietal pleura than in those with, for example, far advanced tumor spread on the pleura. The different sensitivities to pain can be observed already during performance of local anesthesia or later when taking biopsies, and accordingly the pain medication can be adapted.

A good sedation in addition to local anesthesia is essential for the following reasons: to improve patient comfort, to suppress pain, to induce amnesia of the procedure, and to improve conditions for the physician by preventing motor reactions and diminishing cough reflexes.

The best "premedication" is a comprehensive explanation of the procedure to the patient, starting with pneumothorax induction to the postthoracoscopic phase. All details that worry the patient should be explained, including chest pain and chest drain placement. Premedication is optional with atropine to minimize the chance of vasovagal reactions and/or with hydrocodone to suppress coughing (which, combined with midazolam, markedly reduces cough during flexible bronchoscopy without causing significant desaturation).

Once the patient is in the decubitus position, usually in the lateral decubitus position with the healthy side up (Fig. 59.10), an ECG monitor, intravenous fluids of normal saline on the arm opposite the procedure, automated blood pressure cuff, and pulse oximetry are placed (SaO_2 is noted in the decubitus position before sedation as well as before and after placement of a nasal oxygen prong).

The induction of medication is performed during cleaning and preparation of the operating field. It consists of a combination of an analgesic (e.g., morphine, demerol, or fentanyl) and/or a sedative (e.g., propofol, midazolam). The medication should be titrated to patient comfort without compromising respiration. All drugs and equipment for cardiac and airway management should be easily accessible on a resuscitation trolley.

After selecting the point of entry, local anesthesia has to be administered carefully step by step (skin, subcutaneous tissue, and intercostal muscle down to parietal pleura and at the caudal rim of the upper and the cranial rim of the lower rib to anesthetize the intercostal nerve as well as the periosteum of the ribs) while taking care, by repeated aspiration, that the tip of the needle is not located in the adjacent intercostal artery.

Performance of MT/P

The physician and the assistant nurse clean their hands with the standard surgical scrub technique and then put on a sterile gown and gloves. The patient's skin is prepared by shaving and disinfecting a large area to include from the sternum to the clavicle and across the axilla past the scapula, to the spinous processes, and down to the base of the thorax. Then, the patient is covered with sterile sheets. Usually, the thoracoscopist faces the patient during the procedure (but may change the position if needed), while the assistant is across the table.

Then, the following steps are taken: at the selected point of entry (usually near the mid-axillary line), a vertical incision is made with the scalpel through the skin and subcutaneous tissue, appropriate to the size of the trocar tube used, usually of approximately 10 mm, parallel with and in the middle of the selected intercostal space. Then, the trocar is inserted in a corkscrew motion until the sudden release of resistance is felt while holding the handle of the trocar firmly in the palm of the hand, while the extended index finger, for safety's sake, limits the depth of insertion needed to reach the pleural space, previously established with the local anesthetic needle. Once the trocar is in the pleural cavity, the trocar is removed and the cannula should lie 1–3 cm within the pleural cavity and be held in position by the assistant. Then, the thoracoscope is placed in the cannula and advanced into the pleural cavity under direct vision through the trocar (Fig. 59.11). If necessary, the pleural fluid is removed with a suction catheter or directly through the working channel of the semirigid pleuroscope. In case of a large pleural effusion, the fluid should be

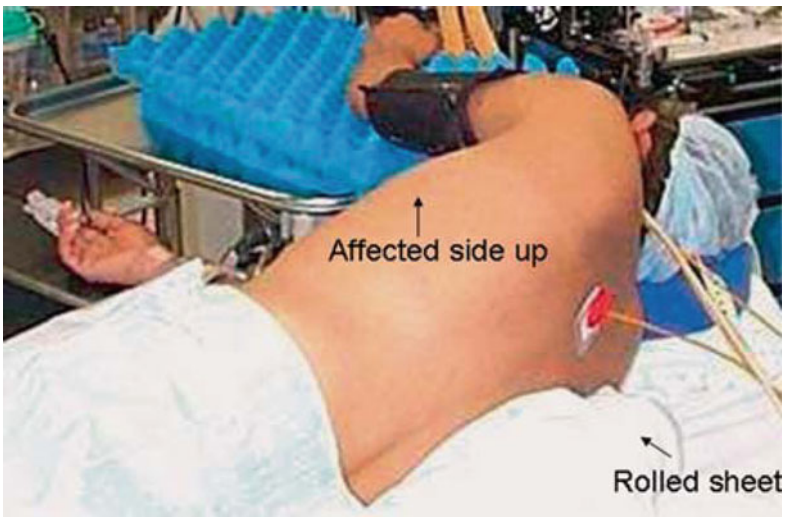

Fig. 59.10 Patient lying in the lateral decubitus position with the healthy side up; the head rests on a pillow; the arm is raised over the head with the help of a sling; a rolled-up sheet is placed on the table under the patient's flank; the axillary roll protects the brachial plexus (Reprinted with permission from Loddenkemper R, Mathur PN, Noppen M, Lee P. Medical thoracoscopy/pleuroscopy: manual and atlas. Stuttgart: Thieme; 2010)

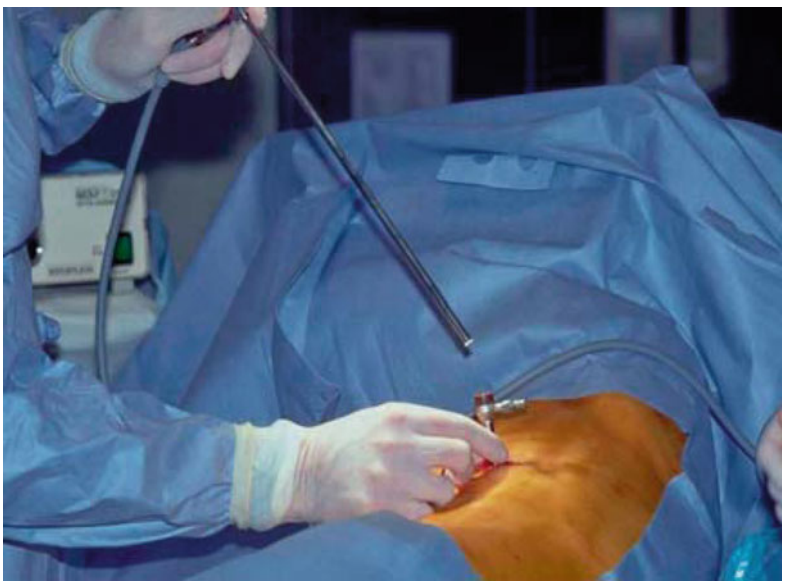

Fig. 59.11 Introduction of the rigid thoracoscope through the trocar (Reprinted with permission from Loddenkemper R, Mathur PN, Noppen M, Lee P. Medical thoracoscopy/pleuroscopy: manual and atlas. Stuttgart: Thieme; 2010)

aspirated completely and not too hastily. This is without risk of development of immediate re-expansion edema, as long as air is allowed to enter the pleural space to replace the aspirated volume, thus maintaining normal intrapleural pressure.

The pleural space can be inspected through the thoracoscope/pleuroscope, either directly or indirectly by video. The endoscope is advanced toward the back and directed toward the diaphragm and the costophrenic angle. After completely removing the fluid, a systematic exploration of the chest cavity is performed by maneuvering the thoracoscope. In difficult cases, oblique telescopes are valuable to ensure adequate pleural inspection with the rigid endoscope.

Orientation is simple, although sometimes fine adhesions resembling spider webs may interfere with complete examination of the pleural cavity. These can be mechanically separated. However, fibrous bands or vascular adhesions should be avoided and can, if necessary, be cauterized by electrocautery.

Anatomical relationships and intrathoracic structures are usually well recognized: orientation on the right can be achieved by locating the point where the three lobes meet, the junction of the oblique fissure and horizontal fissure; on the left, the oblique fissure can be used for orientation. The diaphragm can be recognized because of the respiration-related movement; ribs, intercostal muscles, fat, blood vessels, and nerves are usually well distinguished. The position of the large vessels such as, on the left, the aorta and subclavian vessels and, on the right, the vena cava and the innominate vein as well as the subclavian artery is readily recognized. The heart and the great vessels are identified due to the pulsation, occasionally transmitted to adjacent parts of the lung.

The lung looks like a cone, narrowing at the apex. Variable adhesions between the visceral and parietal pleura may be seen. When the lung is normal, the surface is pink and soft, with a reticular pattern demarcating the pulmonary lobules, and black anthracotic pigment is scattered over the surface. The visceral pleural surface is transparent. Areas of atelectasis are purplish-red with a clear edge. Malignant nodules and other typical pathologies are quite easily seen, as are emphysematous blebs/bullae protruding from the lung surface. One of the hardest tasks for the endoscopist is to distinguish between innocuous inflammation and malignancy.

Suspicious areas are biopsied through the working channel of the thoracoscope/pleuroscope. Often, multiple biopsies are necessary. If lesions are present on the parietal pleura, rather than visceral pleural lesions, these should be biopsied, thus avoiding the risk for prolonged air leak. Typically, 2–6 biopsies of a suspicious pleural lesion will establish a diagnosis. Sufficient quantities of tissue must be obtained, especially if hormonal receptor studies are required for tumors such as carcinoma of the breast. In the presence of undiagnosed pleural effusions, biopsies should be taken at a minimum for microscopically suspicious lesions at the anterior and posterior chest wall and the diaphragm for histological evaluation and, if suspicious for tuberculosis, also for mycobacterial culture.

When malignancy is suspected but the endoscopic findings are nonspecific, the total number of biopsies should be increased up to 10–12 from a variety of areas of the pleural surface. In the future, autofluorescence as well as narrow-band imaging might be helpful in identifying suspicious areas.

Evaluation of Specimens

The pleural fluid should be sent for customary chemistry, cytology, possible tumor markers, and infectious cultures. The cytological examination of pleural effusions should be undertaken by experienced cytologists (biopsies and smears are easier to evaluate and provide a more reliable opinion). The best biopsy specimen should be sent to pathology for processing. If TB or other infections are suspected, biopsies of the parietal pleura as well as fibrinous tissue should be sent for TB bacteriology and fungi and/or anaerobic organisms. Material for electron microscopy should be put in cooled glutaraldehyde.

If the indication for pleurodesis is present, thoracoscopic talc pleurodesis should be performed as best conservative method (see Chap. 63).

Chest-Tube Care

At the conclusion of the procedure, a chest tube is inserted to drain residual air and fluid from the pleural cavity, allowing the lung to re-expand.

The indications for removal of chest tubes placed for various pathological processes are as varied as the indications for tube placement. In general, absence of air leakage and cessation of fluid flow are reasonable guidelines.

Documentation

Documentation of the procedure is essential since it not only provides information to colleagues – chest physicians, oncologists, pathologists, thoracic surgeons, and others – but it is also a permanent part of the patient's medical history. It consists of a handwritten or (better) typed report in which details of the procedure and of the abnormal findings should be included. These should be supplemented, if possible, by endoscopic photographs and/or video recordings. Newer systems most often allow both photographs and video. The use of a computerized documentation program is the ideal; these are available not only for bronchoscopy but also for MT/P.

Contraindications

MT/P is a safe procedure with only a few absolute and relative contraindications (Table 59.6). An absolute contraindication is lack of pleural space resulting from extensive adhesions of the pleural layers (e.g., in pleural fibrosis, after infections, or previous pleurodesis), since it is impossible to carry out the procedure if the pleural space has been obliterated. A partial pneumothorax of at least 100–200 ml, or of approximately 2–4 cm in depth, must be present or induced. Otherwise, the thoracoscope/pleuroscope cannot be inserted safely without danger of injuring the lung or other organs. Sometimes this technical difficulty may be overcome by enlarging the skin incision and digitally dissecting the lung away from the chest wall, as described above.

Coagulopathies usually provide only relative contraindications. More severe coagulopathies are a contraindication at least to biopsy procedures that do not allow immediate local control. The platelet count should be in excess of 60,000, and the international normalized ratio (INR) less than 1.2, otherwise a correction of the coagulopathy must be undertaken prior to the procedure. There are no MT/P studies on the risk of bleeding in patients with aspirin or clopidogrel medication. A report on the risk after transbronchial biopsies did not reveal increased bleeding with aspirin. The risk of bleeding is also higher in patients with renal insufficiency and elevated nitrogen urea (>30 mg/dl) or creatinine (>3 mg/dl).

Great care should be taken in the face of hypoxemia, in particular, in the presence of hypocarbia. Depending on the severity of the respiratory insufficiency, this may provide an absolute contraindication. The only exception would be patients with massive pleural effusion or tension pneumothorax, in whom it can be anticipated that the procedure will provide therapeutic benefit with improvement of gas exchange due to re-expansion of the compressed or collapsed lung. Under these conditions, (pre-) medication should be administered judiciously to minimize respiratory center depression. Although these are relative contraindications, inability to adequately collapse the lung away from the chest wall due to intolerable hypoxemia not only limits exploration but also increases the risk of lung injury and bleeding from instrumentation. In such instances, MT/P is not recommended unless good control of airways, respiration, and oxygenation can be achieved. The same may apply if the patient does not tolerate the lateral decubitus position. However, even in very ill patients on a ventilator, MT/P can be performed without significant complications.

Several other factors may make it necessary to postpone the procedure, but are rarely prohibitive, for example, persistent cough, fever, or an unstable cardiovascular status.

MT/P should not be performed following a recent myocardial infarction or in the face of serious arrhythmia, unless the latter is due to marked hypoxemia as in patients with tension pneumothorax. The patient should be free of infection, unless a parapneumonic effusion or empyema is present, which provides a therapeutic indication to carry out MT/P.

Contraindications for pulmonary biopsy are suspicion of arteriovenous pulmonary aneurysm, vascular tumors, and hydatid cysts. Taking biopsy samples of honeycomb lung from end-stage pulmonary fibrosis should also be avoided as it contributes to a high incidence of bronchopleural fistula.

A markedly reduced general health status with an expected short survival should exclude performance of the examination unless it is likely to improve the patient's situation – for example, in case of pneumothorax or empyema.

MT/P should be performed as an invasive procedure only when other, simpler methods fail to yield a diagnosis or when less invasive therapeutic measures are not available or less promising. For each individual, the risk-benefit ratio must be considered. Therefore, careful evaluation of the patient as well as of the indications and contraindications to the procedure is mandatory. MT/P is safe if the patient is evaluated carefully, the thoracoscopist is adequately trained, the contraindications are observed, and the complications are prevented.

If convinced, by applying strict criteria, that MT/P is indicated, the physician should have little difficulty explaining the need for the procedure to the patient and obtaining informed consent. To be certain that the patient fully understands what is to be done and why the procedure is necessary, a handout with detailed explanation of the procedure should be provided, followed by verbal explanation and discussion. This includes an explanation of the planned technique, the management of postoperative pain, and other possible, so-called typical complications, as well as the expected diagnostic or therapeutic results. It is only then that the patient can truly provide informed consent.

Table 59.6 Absolute and relative contraindications to medical thoracoscopy/pleuroscopy

Absolute	Relative
Lack of pleural space due to:	Inability to tolerate lateral decubitus position
Advanced empyema	
Pleural thickening of unknown etiology	Unstable cardiovascular or hemodynamic status
Suspected mesothelioma where the visceral and partial surfaces are fused	Presence of severe, uncorrectable hypoxemia despite oxygen therapy
	Bleeding diathesis
	Pulmonary arterial hypertension
	Refractory cough
	Drug hypersensitivity
	Reduced general health status with short suspected survival

Source: Reprinted with permission from Loddenkemper R, Mathur PN, Noppen M, Lee P. Medical thoracoscopy/pleuroscopy: manual and atlas. Stuttgart: Thieme; 2010

Complications and Their Prevention

MT/P is a safe and effective modality in the diagnosis and treatment of several pleuropulmonary diseases if certain standard criteria are fulfilled. The advantages of the technique should be weighed against the discomfort of the patient and the slight potential for morbidity and mortality. Although the risks are low, it is important that adequate precautions are taken, including the recommended technical procedure as well as monitoring of cardiac and hemodynamic parameters and oxygen saturation during the procedure.

As for all conscious sedation protocols, patients undergoing MT/P should refrain from eating and drinking 6–8 h before the procedure to reduce the risk of aspiration.

Complications that may be associated with MT/P can be separated into those that may occur before, during, or after the procedure (Table 59.7).

Embolism. The most serious complication of pneumothorax induction is air or gas embolism that can occur during pneumothorax induction. Fortunately, it happens very rarely (<0.1 %) and can be prevented if appropriate precautionary methods are taken.

Pain. The patient may experience short pain during penetration of the parietal pleura by the pneumothorax needle or during local anesthesia. Additional pain may occur in patients with dense adhesions, but this is always associated with an increase in intrapleural pressure since the lung cannot collapse sufficiently. In the presence of effective local anesthesia and well-titrated sedation, little discomfort is felt, even when instruments with a large diameter (11 mm) are used. When biopsies of the parietal pleural are taken, patients must be warned of the associated brief discomfort and should be advised that they may cough when the lung is biopsied.

Prior to talc insufflation, which may be painful, additional analgesics (alternatively intrapleural lidocaine spray) should be given to the patient.

Hypoxemia. The procedure may cause hypoxia for several reasons: depression due to the anesthesia, healthy lung in the lateral decubitus position, and collapse of the investigated lung due to the induced pneumothorax. Oxygen saturation usually decreases only insignificantly during the procedure; nasal oxygen may be provided prophylactically.

Hypoventilation. Some advocate the simultaneous cutaneous measurement of carbon dioxide (P_cCO_2) since significant hypoventilation might occur due to the sedation.

Cardiac Arrhythmias. Except for a slight sinus tachycardia, cardiac arrhythmias are rare.

Hypotension. With the removal of large pleural effusions, one should be alert to the development of hypotension because of the associated considerable volume loss. Some authors recommend atropine to suppress vasovagal reflexes, but it is not clear whether atropine is necessary as a routine premedication.

Hemorrhage. A major concern often expressed regarding MT/P is the risk of bleeding and the need for surgical backup. In this regard, the reported incidence of significant bleeding – that is, requiring transfusion or surgical intervention – is exceedingly low. Superficial bleeding at the site of entry ceases as a result of compression following introduction of the trocar. If hemorrhage occurs after the taking of biopsies, this is in general only very slight and ceases spontaneously if the suggested precautions are observed. If bleeding does not stop or if an intercostal vessel has been biopsied inadvertently, the bleeding area should be compressed and/or cauterized with electrocoagulation.

Table 59.7 Potential complications of medical thoracoscopy/pleuroscopy before, during, and after the procedure

Prethoracoscopic/prepleuroscopic complications	Complications during thoracoscopy/ pleuroscopy	Postthoracoscopic/postpleuroscopic complications
Air embolism, subcutaneous emphysema, and pain during pneumothorax induction	Pain	Re-expansion pulmonary edema
	Hypoxemia	Pain
Shortness of breath after pneumothorax induction	Hypoventilation	Postoperative fever
	Cardiac arrhythmias	Wound infection
Hypersensitivity reaction to local anesthetic	Hypotension	Hypotension
	Hemorrhage	Empyema
	Injury to lung or other organs	Subcutaneous emphysema
		Persisting pneumothorax
		Prolonged air leakage
		Continuing pleural fluid production
		Early and late complications after talc pleurodesis
		Seeding of chest wall by tumor cells
		Mortality

Source: Reprinted with permission from Loddenkemper R, Mathur PN, Noppen M, Lee P. Medical thoracoscopy/pleuroscopy: manual and atlas. Stuttgart: Thieme; 2010

Injury to Lung or Other Organs. Injury to the lung or other organs is almost always avoided by proceeding carefully, in particular, when adhesions between the chest wall and the lung are present.

Potential postthoracoscopic complications are re-expansion pulmonary edema, pain, postoperative fever, wound infection, empyema, subcutaneous emphysema, persisting pneumothorax, and prolonged air leakage, particularly after lung biopsies with a stiff or trapped lung.

Mortality is reported to be an extremely rare event of MT/P with only one death in 8,000 cases (mortality rate of 0.01).

Complications can best be prevented by observing a few simple rules: postpone for several days if the patient is coughing, measure blood gases, monitor cardiac status, and oxygenate the patient during the procedure. Coagulate and ensure hemostasis if hemorrhage exceeds 20 ml, insert a chest tube until no air leakage is detected to prevent subcutaneous emphysema, start a lung expansion protocol on the day of MT/P to prevent atelectasis, and start gentle suction to avoid re-expansion pulmonary edema. To prevent invasion of the insertion track of the thoracoscope in malignant mesothelioma, consider radiation therapy of 7 Gy per day for 3 days to the incision area (if thoracentesis or closed needle biopsies were taken, their tracks may also receive radiation), although this is controversial.

Indications

MT/P is today primarily a diagnostic procedure, but it can also be applied for therapeutic purposes (see Table 59.2). Pleural effusions are by far the leading indication for MT/P both for diagnosis, mainly in exudates of unknown etiology, and for staging in diffuse malignant mesothelioma or lung cancer and for treatment by talc pleurodesis in malignant or other recurrent effusions. It may be helpful also in the early stages of empyema (see Chaps. 64 and 66). Staging of spontaneous pneumothorax combined with local treatment, in stages I and II, is also an excellent indication (see Chaps. 63 and 64). Those who are familiar with the technique can use it, for example, for biopsies from the diaphragm, the lung, the mediastinum, and the pericardium or for sympathectomy (see Chap. 64). In addition, MT/P offers a remarkable tool for research as a "gold standard" in the study of pleural effusion and pneumothorax.

The indications for diagnosis in localized lung and chest-wall lesions have diminished considerably because imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) very often deliver the diagnosis or allow differentiation between malignant and benign disease. In addition, VATS or "surgical thoracoscopy" can be performed by preference in these indications for diagnosis and for simultaneous removal of the lesion (see Chap. 65).

Furthermore, the indications for thoracoscopic/pleuroscopic lung biopsies in diffuse lung diseases have decreased. This decrease is due to the improved diagnostic results of bronchoscopy using transbronchial lung biopsies and bronchoalveolar lavage as well as to the development of high-resolution CT (HRCT), which improves the definition of structural changes and sometimes even gives the diagnosis (e.g., in pulmonary Langhans cell histiocytosis).

Advantages of MT/P in the diagnosis of pleural effusions are a fast and definite biopsy diagnosis including TB culture and hormone receptor assay; biopsies not only from chest-wall pleura but also from diaphragm, lung, and mediastinum; staging in lung cancer and diffuse mesothelioma; and exclusion of malignancy and tuberculosis with high probability (Table 59.8).

Advantages of MT/P in the treatment of pleural effusions are complete and immediate fluid removal and evaluation of loculations (TB, empyema) and of the re-expansion potential of the lung. In addition, talc poudrage for pleurodesis can be performed with uniform distribution of talc under visual control (see Chap. 63) (Table 59.9). Due to a fast diagnosis, drug treatment, for example, in TB, can be started early. The important role of MT/P in the management of malignant pleural effusion is described in Chap. 67. Besides the high diagnostic sensitivity and specificity (Fig. 59.12), MT/P can be combined with talc poudrage, providing an even distribution of the talc powder to all parts of the pleura by poudrage under visual control. In tuberculous pleural effusions, MT/P has the highest diagnostic accuracy and, most importantly, allows the cultural proof of growth of TB bacilli more often, which gives a higher chance to determine drug resistance (Table 59.10). In our opinion, it is questionable whether patients in low-incidence areas of tuberculosis should undergo treatment with antituberculous drugs merely on the suspicion of a tuberculous etiology of the pleurisy. In these cases, we recommend MT/P to prove or exclude TB. In addition, the immediate, complete drainage of the pleural fluid, achieved during and after MT/P, is associated with greater and direct symptomatic improvement than is any subsequent therapy.

Table 59.8 Advantages of medical thoracoscopy/pleuroscopy in the diagnosis of pleural effusions

Fast and definite biopsy diagnosis including TB culture and hormone receptor assay
Biopsies not only from chest-wall pleura but also from diaphragm, lung, and mediastinum
Staging in lung cancer and diffuse mesothelioma
Exclusion of malignancy and tuberculosis with high probability
Gold standard for scientific studies

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Table 59.9 Advantages of medical thoracoscopy in the treatment of pleural effusions

Complete and immediate fluid removal
Evaluation of loculations (TB, empyema)
Evaluation of the re-expansion potential of the lung
Talc poudrage for pleurodesis with uniform distribution of talc (6–10 ml) under visual control (= nonsurgical gold standard)
Early start to drug treatment, for example, TB
In addition, better diagnosis + staging

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Table 59.10 Yield (%) of different biopsy methods in tuberculous pleural effusions (cultural and histological results combined). Prospective simultaneous comparison (n = 100)

Biopsy method	Culture	Histology	Culture and/or histology
Pleural effusion (PE)	28	–	28
Needle biopsy (NB)	25	38	51
PE + NB	39	38	61
Med. thoracoscopy/ pleuroscopy (MT/P)	76	94	99
MT/P + PE	78	94	100

Source: Data from Loddenkemper et al. Prax Klin Pneumol. 1983;37:1153–1156

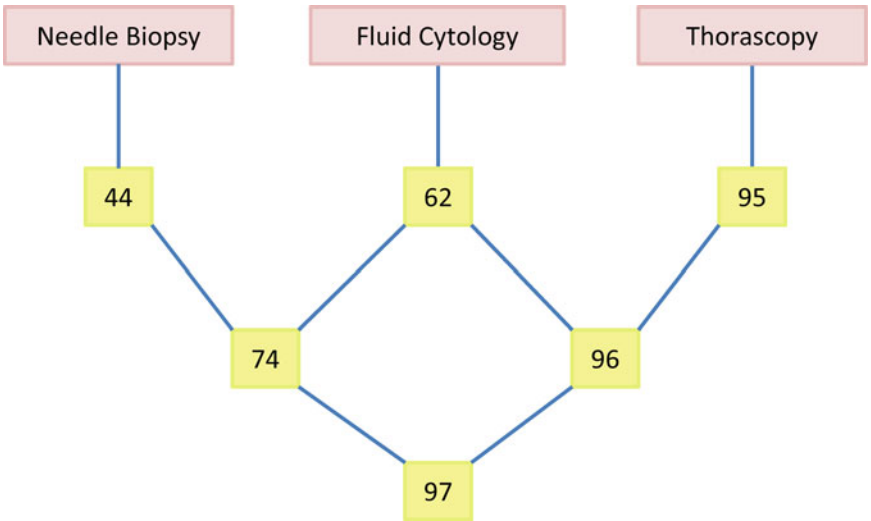

Fig. 59.12 Sensitivity (%) of different biopsy methods in malignant pleural effusions (prospective simultaneous comparison, $n = 206$) (Reprinted with permission from Loddenkemper R, Mathur PN, Noppen M, Lee P. Medical thoracoscopy/pleuroscopy: manual and atlas. Stuttgart: Thieme; 2010)

In other pleural effusions, when the origin remains indeterminate, the main diagnostic value of MT/P lies in its ability to exclude with higher probability malignant or tuberculous disease. In some cases of pleural effusions that are neither malignant nor tuberculous, MT/P may occasionally give macroscopic clues to their etiology, for example, in rheumatoid effusions, in pleural effusions due to liver cirrhosis or pancreatitis, and in rare etiologies, such as amyloidosis or sarcoidosis.

MT/P is helpful in differentiating between malignant and paramalignant pleural effusions in lung cancer, and it is well suited for diagnosis of benign, asbestos-related pleural effusions, which, by definition, present a diagnosis of exclusion.

In some selected cases of recurrent pleural effusions of nonmalignant etiology, including chylothorax, hepatic effusions, and refractory effusions due to cardiac etiology or in systemic lupus erythematosus, talc poudrage during MT/P may be successfully applied.

When MT/P is used in the diagnostic workup of pleural effusions, the proportion of so-called idiopathic pleural effusions usually falls markedly below 10 %. Follow-up studies in those pleural effusions of indeterminate origin have shown that only 4–8 % of the "idiopathic" cases developed malignancy, mostly malignant pleural mesothelioma or malignant lymphoma. Autofluorescence videothoracoscopy or narrow-band imaging during MT/P may help in the future to avoid some of the false-negative results. In addition, in indeterminate cases, repeated MT/P is feasible.

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Pleurodesis

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Julius Janssen

Pleurodesis

Definition and Mechanism of Action

Pleurodesis is defined as symphysis of the parietal and visceral pleura. The pleurodesis is caused by formation of fibrotic tissue in the virtual interpleural space. The fibrosis is caused by fibrin production of the parietal pleura, as a reaction to inflammation, which in turn is caused by a chemical or mechanical agent.

After instillation of a pleurodesis agent, an inflammatory response is initiated resulting in the formation of fibrosis between the parietal and visceral pleura. Fibroblast growth factors, especially basic fibroblast growth factor, play a key role in successful pleurodesis. Basic fibroblast growth factor is produced by normal mesothelial cells. For successful pleurodesis, it is necessary that a significant area of normal mesothelium is still remaining. This is consistent with the clinical observation that pleurodesis is more successful early in the course of malignant pleural disease than in advanced stages.

Indications for Pleurodesis

Pleurodesis is indicated to prevent collapse of the lung due to intrapleural accumulation of fluid or air. The most common indications for pleurodesis are malignant pleural effusion and pneumothorax. Pleurodesis may be indicated in some cases of benign pleura effusion.

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Malignant Pleural Effusion

Malignant pleural effusion is in the clinical setting the most frequent indication for pleurodesis. For the best results, pleurodesis should be performed early in the disease, when trapped lung has not developed yet and the patient is still in an acceptable performance status (see paragraph "optimal timing for pleurodesis"). An initial therapeutic thoracocenthesis will predict the success of pleurodesis to some extent: after evacuation of the pleura effusion, relief of dyspnoea and complete re-expansion of the lung on the chest X-ray are indicators of successful pleurodesis.

Ipsilateral mediastinal shift on the chest X-ray indicates that the dyspnoea of the patient is not caused by malignant pleural effusion but primarily by diseased lung parenchyma (trapped lung, atelectasis, endobronchial obstruction). These patients will rarely benefit from pleurodesis; therapeutic thoracocenthesis will not lead to relief of dyspnoea.

Pneumothorax

Pleurodesis is indicated in primary pneumothorax to prevent recurrence. Although the recurrence rate after the first episode of pneumothorax is +/− 30%, pleurodesis is performed only in recurrent pneumothorax in many countries. In secondary pneumothorax, pleurodesis is mostly performed after the first episode. Talc pleurodesis is the most efficacious form of chemical pleurodesis, with a recurrence rate <5%. According to recent studies, the use of large particle size talc is safe. Long-term follow-up studies also showed that talc pleurodesis has little influence on pulmonary function.

The result of talc pleurodesis is obtained from thoracoscopy/talc poudrage series. There are no data published about the use of talc slurry in pneumothorax. Insufflation of 2 g of talc is sufficient for pleurodesis. The procedure should be performed under general anaesthesia because talc pleurodesis of the visceral pleura is very painful.

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Benign Pleural Effusions

The majority of benign pleural effusions are caused by diseases of the heart, liver or kidney. Pleurodesis is the last option if all other treatments have failed. A trapped lung should be excluded before pleurodesis is attempted. In cases of hepatic hydrothorax or Meigs syndrome, pleural effusion is caused and maintained by transdiaphragmatic flow of ascites fluid. Detection of diaphragmatic defects with coloured Doppler ultrasonography may be followed by thoracoscopic closure of the defect. In these cases, pleurodesis can be much more efficacious due to the reduction of transdiaphragmatic flow of the ascites.

Sclerosing Agents for Chemical Pleurodesis

The ideal sclerosing agent is cheap, safe and widely available and does not cause pain or side effects after intrapleural application. None of the existing pleurodesis agents meet all of these criteria.

Below, the sclerosing agents for pleurodesis which are available on the market today are discussed.

Talc

Of all available sclerosing agents, talc is considered as the best option. It is cheap and widely available. Compared with other agents for chemical pleurodesis, talc gives the best results in terms of effectiveness with least recurrence of effusion in malignant pleuritis (success rate 90%). Talc can be applied as powder, via atomiser (talc poudrage) during thoracoscopy (Figs. 60.1 and 60.2), or can be instilled as a suspension through a test tube (talc slurry). See paragraph on talc slurry and talc poudrage for further details.

Talc is a mineral in its pure form and is defined as hydrated magnesium silicate. Pure talc does not exist; it is mined throughout the world in open pits. Depending on the deposit were talc is found, it is contaminated with associated minerals like chloride (magnesium and aluminium silicate) and calcite (calcium carbonate). Because of the different geologic circumstances of talc formation, ever talc deposit is unique in morphology, varying from highly lamellar tot compact.

Talc and Asbestos

In the past, there was some concern that intrapleural talc could lead to mesothelioma due to asbestos contamination. The association of talc and asbestos is mainly based on overly broad definition of asbestos and non-specific analytical techniques. The geologic conditions under which talc and asbestos form are dissimilar. Besides, the manufacturer of talc confirms that the product is free of asbestos contamination by X-ray diffraction or infrared spectrophotometry.

There is no ground for any fear of asbestos contamination of medical talc; long-term follow-up studies after talc pleurodesis never showed mesothelioma or an increased incidence of other pleural malignancy.

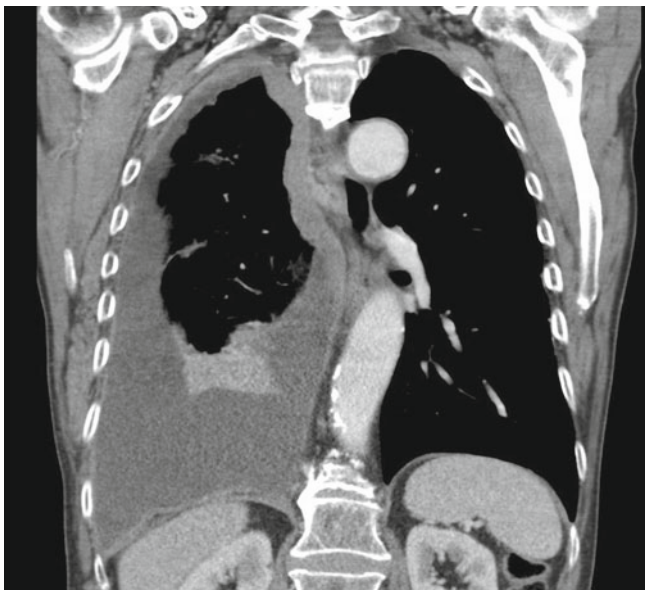

Fig. 60.1 CT scan of mesothelioma on the *right side*. The right lung is surrounded by pleural tumour, and the *middle* and *lower* lobe are compressed by pleural effusion

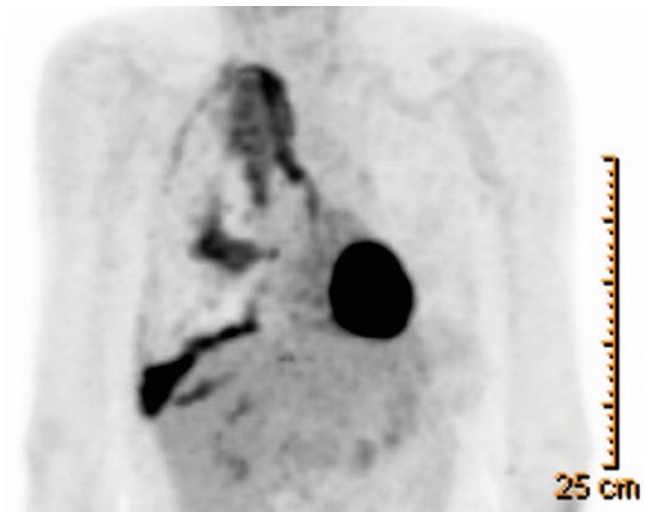

Fig. 60.2 PET scan of the same patient, showing enhanced uptake of the pleura, especially at the level of the mediastinum and pleura

Safety of Talc Pleurodesis: Relation to Particle Size

After incidental reports of early complication after talc pleurodesis, most important ARDS with sometimes fatal outcome, doubts rose about the safety of intrapleural instillation of talc. Despite these concerns, talc was widely used for pleurodesis, and large series including a total of almost 1,000 patients reported no complications after talc pleurodesis.

In experimental studies, the relation between small size of talc particles and inflammation or necrosis of the lung parenchyma was demonstrated. In a clinical study, a relation was demonstrated between pulmonary inflammation and small talc particle size. Increased lung inflammation was found after small particle size talc pleurodesis.

In a prospective cohort study including 558 patients in 14 centres in 11 countries, talc pleurodesis for malignant pleural effusion was performed with exclusive use of large particle size talc (of French origin). No ARDS or other severe complications were found in this study. After talc poudrage, a slight increase in oxygen supply, which was significant during the first 48 h after thoracoscopy, was noticed. Besides, a slight but significant rise of temperature was found in the first 4 days after thoracoscopy and talc poudrage.

Both side effects were clinically insignificant, and the use of large particle size talc for malignant pleural effusion has been considered as safe since the outcome of this study.

All clinicians performing pleurodesis should have knowledge of the particle size of the talc they use. Small particle size talc or medical talc without known particle size should not be used for pleurodesis in humans.

Alternative Agents for Chemical Pleurodesis

Bleomycin

Bleomycin is an anti-neoplastic agent, but its mechanism of action after intrapleural installation is predominantly as a chemical sclerosant. After systemic absorption, its systemic side effect as an anti-neoplastic agent (myelosuppression) is minimal. The technique of bleomycin application is intrapleural installation of a solution of 60,000 IE in saline. The success rate of bleomycin is around 60% in malignant pleural effusion, which is inferior to results obtained with talc. Depending on patent regulations, bleomycin is expensive in some countries.

Tetracycline and Doxycycline

Tetracycline used to be a popular agent for chemical pleurodesis, until production ceased in many countries. The results of tetracycline pleurodesis was slightly inferior to talc. Doxycycline has been tried as an alternative. The efficacy of doxycycline for pleurodesis has been demonstrated in animal studies. However, severe local effects were found. The availability of clinical data with doxycycline pleurodesis in humans is limited. A randomised trial to compare the efficiency of talc powder and doxycycline for pleurodesis in malignant pleural effusion was terminated prematurely, because an interim analysis showed a highly significant difference in favour of talc. Besides, severe respiratory failure in response to doxycycline pleurodesis has been described. The place of doxycycline as an alternative chemical agent for pleurodesis is therefore limited.

Iodopovidone

Iodopovidone is a topical antiseptic. It has been reported as a promising pleurodesis agent, but its mechanism of action is unknown. In a recent study with small numbers of patients, it has shown to be equally effective to talc. Previous studies showed high success rate of 90%. The pleurodesis solution consisted of a mixture of 20 ml 10% iodopovidone and 80 ml normal saline solution. The major side effect was intense pleuritic pain, accompanied by systemic hypotension in 6% of patients. Severe complications were not observed. The advantage of iodopovidone is the wide availability and the low costs.

Silver Nitrate

In a small prospective study, silver nitrate appeared to be equally effective to talc for producing a pleurodesis. Twenty millilitres of 0.5% silver nitrate was injected in the chest tube. There was no difference in pain score between silver nitrate and talc. Silver nitrate is widely available and inexpensive. Most significantly, side effects have been described, but clinical studies with a large number of patients and long-term follow-up are not available.

Talc Pleurodesis: Poudrage or Slurry?

Talc has been accepted as the most effective sclerotic agent in pleurodesis. There are two different techniques of intrapleural administration:

1. Insufflation of dry talc powder into the chest cavity during thoracoscopy, after complete removal of pleural fluid. This treatment is performed in the operation room, under local or general anaesthesia. The advantage of this technique is the combination with the diagnostic thoracoscopy, during which the pleural biopsies can be obtained to assess the specific diagnosis of malignant disease.
2. The other technique is administration of talc slurry (a suspension of talc powder in saline) through a chest tube,

after removal of all, or at least as much as possible pleural fluid, and complete re-expansion of the lung confirmed by chest X-ray. This procedure can be performed at the bedside.

Which of these two techniques provides the best results in talc pleurodesis?

Several studies have addressed this issue in the past decade. In a small-randomised study, no significant difference in recurrence rate was found between talc poudrage and talc slurry. In a porcine study, talc poudrage was performed in one hemothorax and talc slurry in the other in 21 pigs. The animals were sacrificed after 30 days, and both density and distribution of adhesions were scored. Talc poudrage and talc slurry appeared to be equally effective for both density and distribution of adhesions.

A large, prospective randomised trial was published in 2005. Of 501 patients, 242 were randomised to talc poudrage and 240 to talc slurry. The rate of successful pleurodesis after 30 days was equal in both groups, 78% in the talc poudrage group versus 71% in the talc slurry group. However, talc poudrage appeared to be more efficient in the subgroup of breast and lung cancer patients, with a success rate of 82% versus 67% for talc slurry.

In a small, prospective non-randomised study, it was shown that poudrage was significantly more successful than slurry. Successful pleurodesis was immediately obtained in 87.5% of the talc poudrage group, versus 73% in the talc slurry group. Lifelong pleural symphysis was obtained in 82% in the talc poudrage group and 62% in the talc slurry group. In a retrospective study comparing VATS pleurodesis and chest tube pleurodesis in 138 patients, it was found that the recurrence-free survival after VATS was significantly longer than after chest tube pleurodesis. The interpretation of these results is not obvious, as during the VATS procedure both mechanical and chemical pleurodesis was used, and for chest tube pleurodesis not only talc was used but also tetracycline and other mechanical pleurodesis agents.

Unidirectional conclusions and recommendations are not easy to draw from the studies. Talc poudrage seems to be more effective in pleural metastasis in lung and breast cancer, which together represent the majority of patients with malignant pleural effusion. If a diagnostic thoracoscopy is performed for pleural effusion, talc pleurodesis should be performed in case of a malignant appearance of the pleura as the circumstances for pleurodesis after removal of the pleural fluids under visual guidance are optimal.

Talc Pleurodesis Versus Outpatient Treatment with Tunnelled Pleural Catheters

Because of its proven efficacy, talc pleurodesis is the accepted gold standard for treatment of malignant pleural effusion. Outpatient treatment with a permanent tunnelled pleural catheter is reserved for patients with recurrence after chemical pleurodesis, mostly due to trapped lung. In patients with a low performance score and limited life expectancy, a tunnelled pleural catheter may be the treatment option of first choice.

Some authors have suggested a tunnelled pleural catheter as a first-line treatment option for pleurodesis in malignant pleural effusion, under the condition of existing expertise and facilities of outpatient management, because of the high success rate and the limited rate of complications. Tunnelled pleural catheters can be inserted in an outpatient setting under local anaesthesia. Pleural fluid is drained via vacuum bottles in a home-based setting, on a regular or as needed basis. In patients with indwelling pleural catheters, spontaneous pleurodesis may occur, with the recorded success rate of more than 40% in several studies. Recurrence of malignant pleural effusion requiring a repeated invasive procedure is limited less than 9% according to the largest published study of 250 patients. The downside of treatment of malignant pleural effusion with tunnelled pleural catheter is the costs: the vacuum bottles need to be replaced frequently and are expensive. Moreover, in some European countries the vacuum bottles are not reimbursed by health insurance companies. In these cases, the vacuum bottles may be replaced be urinary bags, although there are no published data about the efficacy.

In a recent American study, cost data for PleuRX® and talc treatment were compared using Medicare reimbursement data. Talc pleurodesis appeared to be less costly than PleuRX® treatment, with similar effectiveness. PleuRX® treatment became more effective when life expectancy was 6 weeks or less. Due to the lack of prospective randomised studies, the question, if a tunnelled pleural catheter is equally effective as talc pleurodesis and consequently can serve as a first-line treatment option in malignant pleural effusion, is still unresolved. Pleural-tunnelled catheter is maybe the treatment of first choice in patients with limited life expectancy and may serve as an alternative treatment in case of failure of talc pleurodesis or trapped lung. Besides, local expertise, like the ability to perform thoracoscopy and facilities for home-based care, may influence the optimal choice for treatment with malignant pleural effusion.

Mechanical Pleurodesis

Mechanical pleurodesis is obtained by rubbing of the pleura (abrasion) or removal of the parietal pleura (pleurectomy). Both techniques are invasive surgical procedures and are much less frequently performed than chemical pleurodesis. In an experimental study in dogs, talc poudrage and mechanical abrasion proved to be effective, and pleurodesis results were superior to Nd-YAG laser or argon beam coagulation. In another experimental study, talc (both slurry and poudrage) was superior to abrasion. Two abrasion techniques were used: mechanical abrasion with a dedicated pleural

abrader and focal gauze abrasion by limited thoracotomy. The results of the pleural abrader were unsatisfactory; hardly any pleurodesis was found at autopsy after 30 days. Results of focal gauze abrasion after thoracotomy were better, equal to talc slurry but inferior to talc poudrage.

There are a limited number of studies concerning mechanical pleurodesis in malignant pleural effusion. In a non-randomised study, a success rate of 93% after 6 months was demonstrated for thoracoscopic mechanical pleurodesis. No recurrence was found after thoracotomy with pleurectomy after 6 months. Another study, with a perspective randomised design, compared thoracoscopic mechanical pleurodesis to talc pleurodesis at various pH levels of malignant pleural effusion due to breast cancer metastasis. Mechanical pleurodesis and talc pleurodesis were equally successful in patients with pH levels of 7.3 (92% and 91% success rate). Mechanical pleurodesis was superior to talc pleurodesis when the pH of the pleural effusion was below 7.3 (81% versus 55%).

In spontaneous pneumothorax, pleural abrasion has been performed as an alternative to pleurectomy. One study compared the results of mechanical pleural abrasion to epical pleurectomy in a group of 220 patients. Post-operative air leak rate was similar in both groups. Hemithorax was significantly more frequent in the partial pleurectomy group (7.4% versus 9% for abrasion). There were no differences in late recurrence rate between both groups.

Hepatic hydrothorax is often difficult to treat. In one study, mechanical and chemical pleurodesis were combined with an intraperitoneal drain to prevent re-accumulation of ascites and subsequent flux to the pleural space. The procedure was well tolerated. In this situation, detection and closure of diaphragmatic defects with colour Doppler ultrasonography is promising.

Pleurectomy

Pleurectomy, performed through open thoracotomy or VATS, is a major surgical intervention and should be avoided as much as possible in patients with a limited life expectancy such as malignant effusion. The rare indication is a patient with dyspnoea caused by trapped lung in a good health status and life expectancy of more than 3 months.

The Influence of Anti-inflammatory Drugs (NSAID and Steroids) on Chemical and Mechanical Pleurodesis

Pleurodesis is caused by an inflammatory response of the pleura to a chemical or mechanical agent such as talc or abrasion of the parietal pleura. The inflammatory response leads to the production of fibrin and results in the development of fibrosis, resulting in the symphysis between the parietal and visceral pleura. In theory, the inflammatory response can be inhibited by the use of anti-inflammatory drugs, both steroids and non-steroids. This question has been addressed by several studies; most of these had an experimental design.

In a rabbit study, it was shown that the use of corticosteroids (triamcinolone 0.8 mg/kg) at a time of talc slurry pleurodesis markedly decreased the inflammatory reaction to talc and prevented a pleurodesis from developing.

In another rabbit study, formation of pleural adhesion was significantly reduced after concomitant interpleural injection of 400 mg/kg talc and 1 mg/kg methylprednisolone (sustained for 1 week), compared to intrapleural injection of talc alone. The degree of pleural adhesion was not reduced by corticosteroids when silver nitrate was used as sclerosing agent.

In the same rabbit study, talc pleurodesis was also performed in a subgroup of rabbits with or without concomitant injection of diclofenac 1.1 mg/kg, which was sustained for 1 week. The same result was found for diclofenac as for methylprednisolone. The degree of pleural adhesions was reduced in the talc group but did not affect silver nitrate-induced pleurodesis.

A more recent rabbit study showed no influence on talc or doxycycline pleurodesis during concomitant administration of ketoprofen. COX-2 inhibitors also did not interfere with talc or silver nitrate pleurodesis in rabbits.

In an experimental study in pigs, the influence of NSAIDs (100 mg diclofenac orally for 21 days after surgery) in pleural abrasion was assessed. In comparison with the control group, the quality of pleural adhesions was highly affected by the use of diclofenac.

The animal studies showed that talc pleurodesis is reduced by NSAIDs and corticosteroids, but not by COX-2 inhibitors. It is not clear if these results can be extrapolated to humans. Some experts observed increased failure of talc pleurodesis during simultaneous corticosteroid treatment.

Until more studies will clarify this issue, it is advised for optimal pleurodesis to avoid NSAIDs and corticosteroids and use morphine or low dose COX-2 inhibitors.

Factors of Influence on Success of Pleurodesis in Malignant Pleural Effusion

Optimal Timing of Pleurodesis

Pleurodesis is indicated in patients with dyspnoea due to pleural effusion and a life expectancy of more than 2 months. Risk factors for limited survival (life expectancy < 30 days) are low BMI score (< 25) and poor performance status (Karnofsky < 50%). It remains difficult, however, to estimate survival in an individual patient. A favourable outcome factor

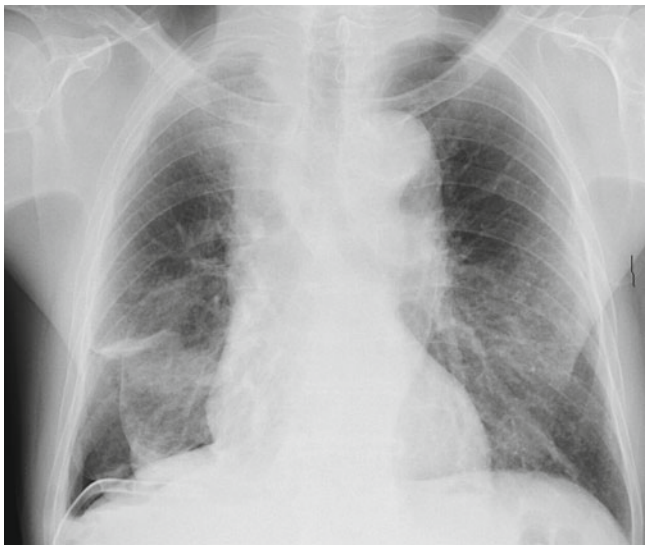

Fig. 60.3 Chest X-ray after thoracoscopy and attempted pleurodesis. The drain is visible above the diaphragm; the lung is trapped, with incomplete re-expansion of the *middle* and *lower* lobe

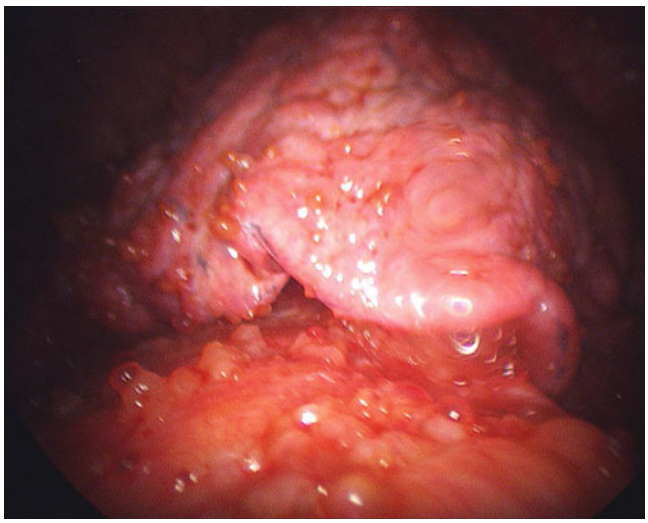

Fig. 60.4 Lung and pericardium covered with tumour nodules, which proved to be mesothelioma after biopsy

for a successful pleurodesis in malignant pleural effusion is a fully expendable lung. Both a good performance score and a fully expendable lung are present early in the course of the disease in most cases. Therefore, patients gain from pleurodesis most if they are treated early in the disease.

Before pleurodesis is performed, the clinician should be convinced that the respiratory symptoms of the patient are caused by the effusion. This can be demonstrated by a relief of dyspnoea after therapeutic thoracocenthesis. Patients with a trapped lung will not gain from pleurodesis (Figs. 60.3, 60.4, and 60.5). It is recommended to make a chest X-ray after therapeutic thoracocenthesis, to assess the rate of lung expansion.

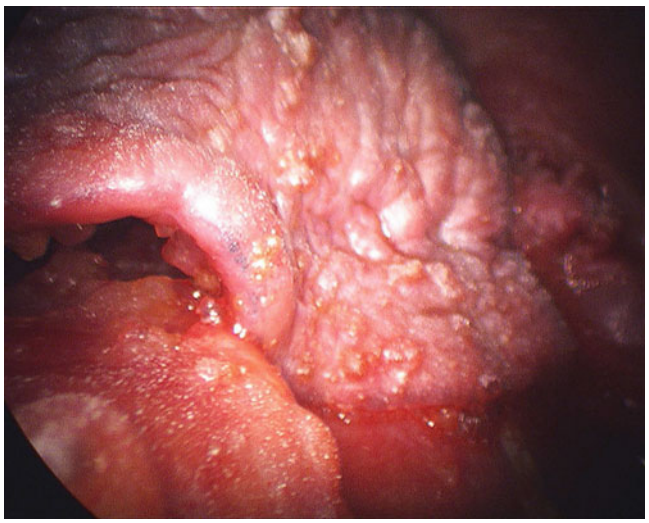

Fig. 60.5 Same as 1, picture taken after talc poudrage

In conclusion, it is recommended to perform pleurodesis as soon as there is evidence of an increasing amount of pleural fluid due to metastatic malignancy. At that time in most cases, the lung is re-expendable, and the performance status of the patient is good.

Tumour Volume

It has been observed that tumour volume is inversely related to the success of pleurodesis. It also has been demonstrated that successful talc pleurodesis was related to the level of basic fibroblast growth factor in the pleural effusion. Basic fibroblast growth factor is produced by healthy mesothelial cells, and they play a critical role in the development of pleural fibrosis. In the same study, a significant negative correlation between basic fibroblast growth factor levels and tumour size was demonstrated. In experimental studies, it was shown that viable talc-exposed mesothelial cells may actively mediate the primary inflammatory pleural response in talc-induced pleurodesis.

These studies suggest that pleural fibrosis depends on a process mediated by healthy mesothelium. The number of normal mesothelial cells is reduced in patients with a large tumour volume, thereby reducing the chance of a successful pleurodesis. The data support the decision to perform pleurodesis early in the disease.

pH

There has been a discussion in the literature about the use of pleural pH in selecting candidates for pleurodesis. In a meta-analysis, it was demonstrated that pleural pH has only modest

value for predicting success of pleurodesis and should be used with caution, if at all, in selecting patients for pleurodesis. In another study concerning mechanical pleurodesis in malignant pleural effusion in breast carcinoma, successful pleurodesis was obtained in more than 50% of patients despite low pleural pH. In our practice, pleural pH is not used for selection of patients for pleurodesis.

Optimal Pleurodesis: How to Handle the Chest Tube?

Size of the Chest Tube: Which Tube to Use?

Conventionally large-bore chest tubes (20 F and more) were used for drainage of pleural fluids and consequent pleurodesis. However, large-bore tubes are associated with discomfort for the patients, and the advantage over small-bore tubes (10–14 F) has never been clearly stated in the available literature. In treatment of malignant pleural effusion, small-bore and large-bore chest tubes appeared to be equally efficacious. It is therefore advised to use small-bore chest tube (10–14 F) in all patients with malignant pleural effusion for fluid removal and pleurodesis.

The Optimal Timing of Pleurodesis in a Patient with Malignant Pleural Effusion and an Intercostal Chest Tube

Although this question is very relevant in the daily clinical treatment of the malignant pleural effusion, the answer is not clear. Evident in the literature is very limited. Traditionally, pleurodesis is performed if the daily fluid production is less than 150 ml/24 h. One small study, using tetracycline as pleurodesis agent, showed that it was more efficacious to perform pleurodesis as soon as full lung re-expansion is obtained. In case of incomplete lung re-expansion, due to trapped lung, it is still worthwhile to perform pleurodesis as a partial successful result can be achieved in some cases.

When to Remove the Chest Tube?

The optimal moment of drain removal after pleurodesis is not known. This question, surprisingly, has rarely been a subject of clinical study in the past. In one small study, 41 patients were randomised for drain removal 24 h versus 72 h after talc pleurodesis. The primary outcome measure was success of pleurodesis. No difference in success rate was found between the two groups. Hospital stay was significantly reduced when the chest drain was removed at 24 h. The same observation was made in a previous study using tetracycline.

A short hospital stay is important in this group of patients with a very limited life expectancy. It is therefore advised to remove the drain within 24 h after pleurodesis or even immediately after pleurodesis (if the lung has re-expanded completely), and not to wait until the volume of the drained pleural fluid has dropped below 150 ml/24 h.

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Advanced Medical Thoracoscopy-Pleuroscopy Procedures

61

Marios E. Froudarakis

Introduction

When the Swedish physician Hanz-Christian Jacobaeus in 1910 introduced a cystoscope into the pleural cavity of a patient with pleural tuberculosis, he could not imagine that he was the starter of thoracoscopy, the oldest invasive diagnostic method applied in the recent history of pneumonology. His operation served to lyse adhesions in order to induce therapeutic pneumothorax. One century later, thoracoscopy has been abandoned as a therapeutic approach for tuberculosis, but it has been implemented in the diagnosis and treatment of a variety of pleural disorders. The method was developed and refined initially in Europe, through this century, and spread worldwide for the benefice of patients with pleural diseases [1]. Actually, this method is the gold standard in the diagnosis and treatment of pleural diseases, with a diagnostic yield of 95% in patients with malignant pleural disease [2], whereas success in pleurodesis is approximately 90% for malignant pleural effusion and 95 % for pneumothorax [1]. Despite the performance of thoracoscopy in diagnosing the cause of pleural effusion, the method has known a continuing development in the recent years in terms of new devices improving its diagnostic yield, as well as, it has been used in clinical and basic research in many disorders involving the pleura [3]. The technique of basic thoracoscopy has been described in another chapter.

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Advanced Techniques in the Development of New Tools and Devices

Minithoracoscopy

More recently, the technique of minithoracoscopy has allowed the use of 4-mm trocar with 3.3-mm telescope and 3-mm forceps in patients with undiagnosed pleural effusion. Thoracoscopy is performed in the endoscopy suite under local anesthesia and/or mild conscious sedation. Visualization using minithoracoscopic instrumentation is excellent allowing thorough inspection of the pleural space. No complications are noted, and patients' tolerance is good in the majority of cases (24 out of 30, 80 %). Main limitations of the technique are difficulties in lyse adhesions and in the average 20 % increase duration of intervention. Also in patients with hemorrhagic effusions, visibility might be diminished, since the diameter of the telescope is small and the light is likely to be absorbed by the bloody effusion and/or pleura. The diagnostic yield of minithoracoscopy was 93 %, equal to classic rigid technique. However, a major advantage of minithoracoscopy over classic thoracoscopy was the excellent cosmetic result [4].

Narrow Band Imaging (NBI) Thoracoscopy

The development of the flex-rigid thoracoscope gave the possibility to use devices reserved until now to fiber-optic devices, showing a possible future development of medical thoracoscopy [3]. The narrow band imaging (NBI) device was used to recognize and determine differences in microcirculations of the tissues between malignant and benign

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diseases of the pleura in patients with undiagnosed pleural effusion [5]. NBI is a new alternative light-wavelength capture system that takes advantage of altered blood vessel morphology and is described in detail in another chapter.

Despite limitations due to the inherent difficulties in performing NBI in such a large cavity with light dispersion, bleeding and/or bloody effusion, and light-reflecting white pleural thickening, this study shows a possible future development of medical thoracoscopy [6]. Using NBI, neoangiogenesis is recognizable in malignant pleural disease by the development of heterogeneous vessel caliber by CD 34 staining of microvascular proliferation [5]. Since molecular staging of malignancies today is becoming a "must" in the expansion of the use of targeted therapy, it is easily understandable that this important observation of Ishida and coworkers may open a new area of research in pleural malignant disease [6].

Autofluorescence Thoracoscopy

Another device used recently to increase diagnostic yield of thoracoscopy is fluorescence [7]. The autofluorescence excitation in the system used in patients with undiagnosed exudative pleural effusion (R. Wolf GmbH, Knittlingen, Germany) is achieved by means of a 300 W xenon lamp in the violet-blue range (390–460 nm). The photodetection system relies on one charge-coupled device (CCD) camera and a dual-detection range (green region of 500–590-nm wavelength and a red region of 600–700-nm wavelength), as at least two spectral domains are necessary for efficient contrast enhancement [7].

The goal is to prove whether the combination of white light thoracoscopy to autofluorescence thoracoscopy can improve diagnostic yield in those patients. Sensitivity is 100 % meaning that in all cases of malignant pleuritis (carcinoma or mesothelioma), the color of the affected area of the pleura changed from white/pink to red. However, specificity is 75 %, as in two cases of chronic pleuritis, a color change from white/pink to orange/red is recorded. The calculated positive predictive value of color change for malignant pleuritis during autofluorescence thoracoscopy is 92 % [7].

Pleural Lavage During Thoracoscopy

In patients with non-small cell lung cancer (NSCLC), visceral pleural invasion is a poor prognostic factor [8, 9]. Invasion of visceral pleura is confirmed by means of a pathologic examination. However, sometimes it is not clear for the pathologist to ascertain visceral pleura invasion by the tumor. In the recent years, authors reported a simple method involving a cytologic examination of cells desquamated from the visceral pleura by using a jet stream of saline solution performing a real pleural intraoperative lavage [8, 9]. This method is considered to be significantly more accurate than ordinary pathology in detecting visceral pleura invasion by lung cancer [8]. Patients with positive cytology from intraoperative pleural lavage showed significantly poorer survival than those with negative cytology [8]. Pleural lavage is possible during thoracoscopy [10]. It has been shown that it provides pleural cytology in normal subjects [10] as well as additional information in combination to thoracoscopy in patients with malignant pleural disease [11]. A step forward in patients with NSCLC and peripheral lesion could be the systematic investigation of pleural cytology and therefore of the possibility of the presence of micrometastatic disease of the pleura otherwise invisible, in order to accurately stage the disease and predict survival of the patient. That might lead to better managing those patients.

Advanced Techniques in the Pathophysiology and Treatment

Pneumothorax

The pathogenesis of primary spontaneous pneumothorax is under debate. Thoracoscopy by using new tools is also applied to investigate the pathophysiology of the disease. Autofluorescence has been used after inhalation of fluorescein to detect bullae in patients with primary spontaneous pneumothorax (Fig. 61.1). Additional findings suggested substantial areas of parenchymal abnormalities. Satellite areas of parenchymal lesions could only be identified by fluorescein-enhanced autofluorescence in normal subjects during thoracoscopy for other causes [12]. The technique consists in inhalation of an aerosolized 10 % fluorescein solution for approximately 10 min under normal tidal volume conditions, 10–30 min before anesthesia induction [12]. The fluorescein aerosol was delivered via a pressure-driven nebulizer attached to a mask. Thoracoscopy is performed with two ports of entry, under total intravenous anesthesia, with single-lumen intubation with high-frequency jet ventilation delivered through the endotracheal tube. The previously described DAFE (Richard Wolf, Knitlingen, Germany) autofluorescence system is used [12].

Another technique applied recently to investigate bullous or emphysematous lesions of the lung parenchyma is infrared thoracoscopy [13]. After general anesthesia and double-lumen intubation, the lung is observed under normal white light and then observed under infrared thoracoscopy with intravenous injection of 3.0 mg/kg indocyanine green. The infrared thoracoscopic images are analyzed with Lumina Vision (Mitani Co, Fukui, Japan) [13].

The lung lesions are demonstrated in white, whereas normal lung tissue was imaged in blue, under infrared thoracoscopy. Also, small bullous lesions are detectable with infrared thoracoscopy because of its clearer visualization compared with white light thoracoscopy. Quantitative color-density

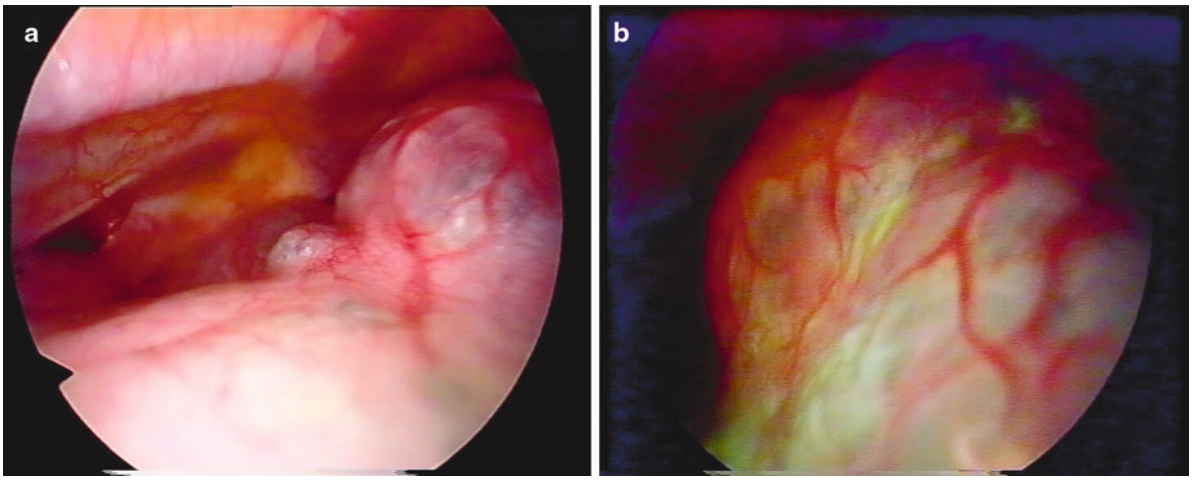

Fig. 61.1 Bulla of the apex in white light (**a**) and after inhalation of fluorescein (**b**) (Courtesy of Prof. Marc Noppen)

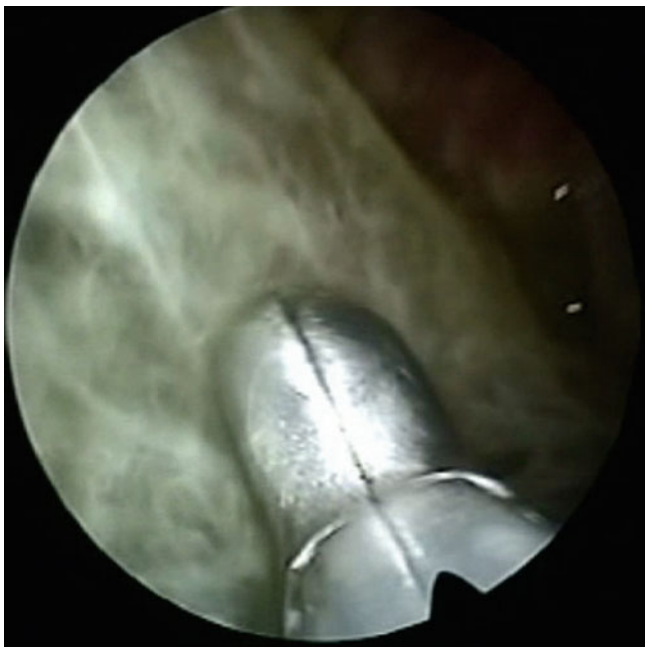

Fig. 61.2 Thoracoscopic view of complicated parapneumonic effusion (multiple loculations)

analysis revealed a marked decrease of indocyanine green intensity, reflecting decreased blood flow of bullous lesions [13]. After injection of indocyanine green, infrared thoracoscopy showed that the area of normal perfusion changed to blue, whereas the area at which perfusion was absent remained white [14]. The transition zone between colors was distinct, and the blue stain remained visible during the marking procedure. Three-dimensional computed tomographic analysis indicated that the marking separated the target segmental bronchus from the adjacent one. Detailed macroscopic and microscopic study confirmed that the marking corresponded to the intersegmental line [14].

Both techniques are a step forward in the understanding of the pathophysiology of primary spontaneous pneumothorax by identifying those lesions otherwise undetectable with the white light technique [6].

Thoracoscopy in Pleural Infection

The place of thoracoscopy in the treatment of pleural infection is not clear. An unsolved issue in the management of patients with pleural infection is whether those patients should undergo early thoracoscopic or simply classical treatment. Thoracoscopy is an alternative to thoracotomy because it allows the mechanical removal of infected material leading to lung reexpansion (Fig. 61.2). Furthermore, the ability to perform pleural biopsies allows the diagnosis of any underlying disease helping the diagnosis of pleural malignancies or other occult infections causing pleural effusion (Fig. 61.3). Mortality in Western countries is about 15 %, while up to 40 % undergo surgical drainage, either video assisted or thoracotomy, with pleural decortication [15]. The goal of pleural infection therapy is to heal the patient, to reduce mortality and morbidity overall hospital stay, and the need of surgical drainage and pleural debridement. Classical treatment associates according to the stage, antibiotics with or without chest tube drainage. The use of fibrinolytics in the treatment of pleural infection is another point of discussion; fibrinolytics have shown to be beneficial in patients with complicated parapneumonic effusion [16], yet their place in empyema is questionable.

For medical thoracoscopy in pleural infection, it is mandatory to choose the point of entry by ultrasonography, to identify the point where the pus collection is largest and the position of the diaphragm, which is often elevated [17]. Once in the pleural space, loculations must be opened with removal

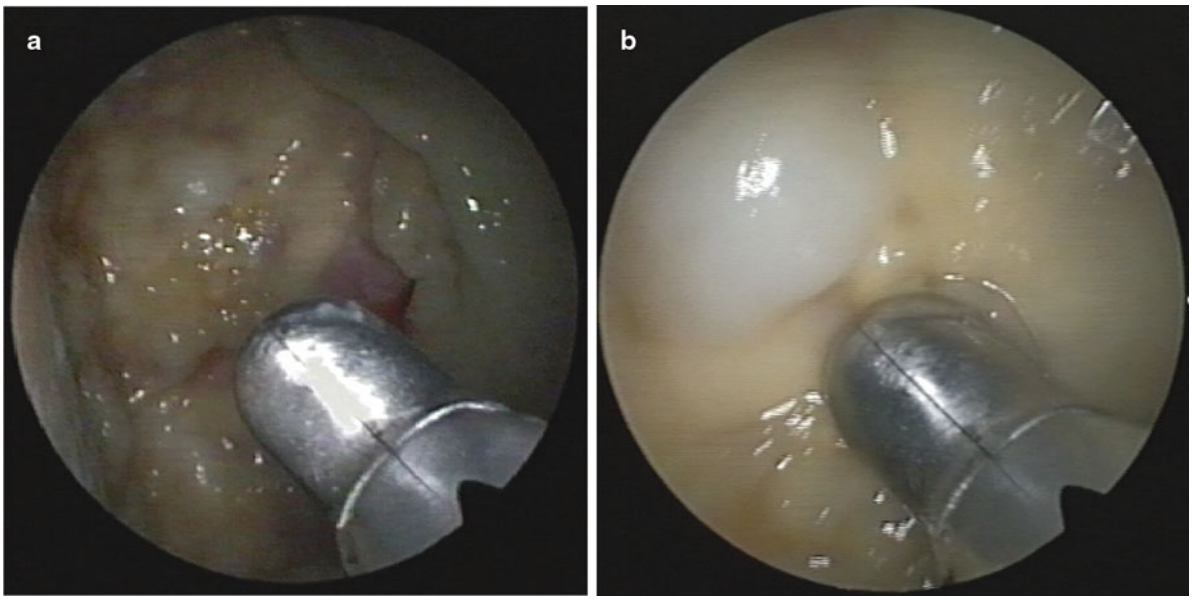

Fig. 61.3 Staphylococcal empyema in a patient with SCLC. (**a**) Thoracoscopy revealed multiple metastatic nodules of the parietal pleura (**b**)

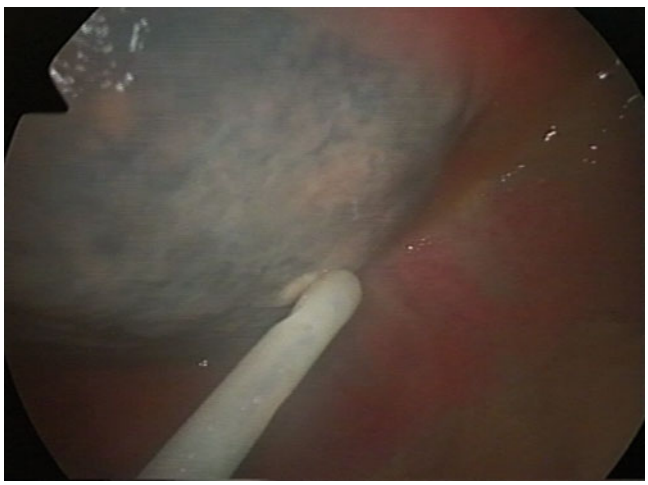

Fig. 61.4 Placement of chest drain under direct vision after thoracoscopic treatment in a patient with empyema

of the fibrinopurulent membranes, aspiration of the liquid, and washing with saline solution. Finally, biopsies must be taken systematically for diagnosis of possible underlying condition favoring pleural empyema (Fig. 61.3). A large-bore chest drain is introduced, better under visual control, to drain pleural cavity and remove dense and viscous pus or fibrin debris (Fig. 61.4) [17].

Reports of thoracoscopy in pleural infections are mainly related to empyema and are principally surgical. They generally describe favorable results, with primary success rates (complete recovery without the need for subsequent or conversion thoracotomy) of 60–100 %. The best results were obtained when the method was applied early in the course of the disease [18]. However, few patients were included in those studies to draw firm conclusions. All studies agree on the advantages of thoracoscopy over thoracotomy because of the less invasive technique, in pain, costs, hospital stays, and cosmetic results. A number of advantages are highlighted for medical thoracoscopy [17]. It is mini-invasive, has lower costs compared with VATS, and is useful in the treatment of patients with comorbidities. Complications are strictly related to case complexity and are mainly represented by air leaks, which are sometimes prolonged, and by bleeding, with incidences of between 16 % and 0 % [17]. Deaths were described in patients with comorbidities [17].

Although early minimal intervention with medical thoracoscopy has shown excellent results in recent reports [19], the need for controlled large phase III trials to further define its place in the treatment of pleural infection is requested. Indeed, the few studies reporting results with small number of patients included are not sufficient to draw firm conclusions.

Thoracoscopy in Sympathectomy

Thoracoscopic sympathectomy techniques are currently standard approaches for sympathectomy. Thoracoscopic sympathicolysis is defined as the anatomical interruption of the thoracic sympathetic chain by thoracoscopy. The level of interruption depends upon the indication and the desired therapeutic effects. Essential hyperhidrosis (palmar, axillar, facial) is treated by interrupting T2 and T3 dorsal sympathetic ganglia [20]. Indications for thoracoscopic sympathectomy might include facial flushing, vascular disorders of the upper limbs (Raynaud's phenomenon, acrocyanosis, arterial insufficiency, Buerger's disease), causalgia, thoracic outlet

syndrome, and cardiac disorders, such as long QT syndrome and chronic pancreatic pain syndromes [17]. Alternatives of thoracoscopic sympathectomy are thoracotomy interruption and percutaneous ablation. However, both techniques are tending to be abandoned, the first because it is invasive and the second because of lower efficacy and higher complication rates [21].

Technique is based on unilateral, or one-time bilateral according to indication, three-entry port thoracoscopy using single-lung, double-lumen ventilation. At the present time, thoracoscopic sympathetic intervention is performed in a 1-day setting, under general anesthesia. The sympathetic chain is located, and electrocautery interruption is performed [20, 21]. Thoracoscopy sympathicolysis can safely be done by trained interventional pulmonologists.

Short – and long-term results are excellent in hyperhidrosis patients. Relief of palmar, axillar, and/or facial sweating is obtained in 90–100 % of cases [20]. Recurrence rates vary between 5 % and 10 %, but repeat interventions are often successful. Complications are rare (<1 %), include Horner's syndrome, pneumothorax, and hemorrhage, sometimes necessitating conversion to thoracotomy. No procedure-related mortality has been reported [20]. Compensatory sweating occurs in the majority of patients after sympathetic interruption and may be related to the level of interruption (T2 interruption increasing its likelihood) and extent (e.g., extensive-level interruption increasing its likelihood). Patients should be extensively informed about the probable occurrence of compensatory sweating. In general, however, this is considered not more than a nuisance and does not affect overall patient satisfaction. However, a small percentage (1–2 %) of patients regret the intervention afterward [22].

Thoracoscopic sympathectomy is a minimally invasive intervention for patients with a variety of autonomous nervous system disturbances. Well-selected patients can be helped by this procedure, performed by either surgeons or pulmonologists. Short – and long-term results are excellent, complications are rare, and side effects are usually limited to a degree of compensatory hyperhidrosis.

Thoracoscopy in the Diagnosis of Lung Diseases

Surgical thoracoscopy under general anesthesia is the method of choice for the diagnosis of parenchymal lesions especially in patients with diffused lung disease (DLD), when bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) have failed [23]. Lung biopsy by such procedure provides large specimens that are virtually identical to those obtained by thoracotomy [24]. However, multiple incisions, costly single-use instruments, and general anesthesia with single-lung ventilation are required. Moreover a conversion from thoracoscopy through mini-thoracotomy is not uncommon due to technical difficulties (deep lung biopsies) and/or complications such as prolonged air leak and/or bronchopleural fistula in case of deep lung biopsies. Thus, lung biopsy under surgical video-assisted thoracoscopy, even in ambulatory patients, is not an entirely benign procedure. Furthermore, it seems that the site, size, number, and laterality of the biopsies in patients with DLD have no definite influence on diagnosis. Careful selection of specific thoracoscopy lung biopsy techniques could result in increased cost-effective diagnosis of pleuropulmonary disorders, less parenchymal lung damage, and lesser morbidity (Table 61.1).

Table 61.1 Comparison of thoracoscopy (VATS) to open thoracotomy for lung biopsy

	Thoracoscopy	Thoracotomy
Intervention time	45 min	−1 h
Hospitalization	2–4 days	3–5 days
Drainage	1–3 days	2–4 days
Biopsy size	2–7 cm	>5 cm
Morbidity	5–10 %	7–12 %
Cost (Euros)	1,500	1,200

Despite encouraging published results in the literature reporting high diagnostic yield of thoracoscopy in patients with DLD using electrocautery lung biopsy [25, 26], most pulmonologists do not use this technique in the diagnostic work-up of DLD. Furthermore, experimental studies showed that multiple small (less than 5 mm) electrocautery lung biopsies were of comparable quality compared to single wedge biopsy specimens obtain by endoscopic stapling [27]. However, many pulmonologists probably still fear the use (and the complications) of pleuroscopy in the diagnosis of lung parenchyma lesions, while many pathologists still have to become acquainted with the smaller amount of tissue compared to the larger surgical samples [25]. The yield could be significantly improved by using under CT a needle or a wire as a hook, to localize lesions before thoracoscopy.

In about 70 % of the cases, accurate diagnosis of DLD is done with the association of patient's clinical history, high-resolution chest computed tomography (HRCT), bronchoalveolar lavage (BAL), and transbronchial biopsy (TBB) [23]. This approach is accurate for patients with pulmonary parenchymal infection, lung fibrosis, sarcoidosis, lymphangitis carcinomatosa, hypersensitivity pneumonitis, amyloidosis, Langerhans cell histiocytosis (LCH), eosinophilic pneumonia alveolar proteinosis, or lymphangiomyomatosis (LAM). Lung tissue is still required for the diagnosis of DLD in approximately 30 % of patients who do not have a clearly defined environmental exposure or obvious systemic illness that frequently involves the lung. The decision to perform lung biopsy in these patients is based on the likelihood that pathologic examination of the tissue obtained will yield specific information about the cause of the disease process and that this information can be used to alter the treatment being received by the patient [23]. The diagnostic accuracy of specimens for DLD depends on the distribution pattern of the

interstitial disease, and thus the lobular compartment involved, and the histological specificity of the disease [28]. It is well known that DLD does not have a uniform spread throughout the whole lung [28]. Thoracoscopy gives the unique opportunity to inspect the whole lung, choose the biopsy areas carefully, and take biopsies from several lobes. The possibility of multiple sampling is an important advantage of thoracoscopy [25]. Consequently, diagnoses such as chronic interstitial pneumonitis either nonspecific (NSIP), usual (UIP) or desquamative (DIP) type, or lung fibrosis could be made with confidence. These diseases are characterized by a widespread involvement particularly of the alveolar compartment [28]. In the same spectrum of "idiopathic" interstitial lung diseases, cryptogenic organizing pneumonia (COP) may also be diagnosed. The existence of polypoid proliferation, involving both the bronchioles and alveolar ducts (organizing pneumonia), leads to the diagnosis of COP, which might be also present in other "idiopathic" entities such as NSIP [28].

Thoracoscopic Treatment of Tamponade

Acute, chronic, or recurrent pericardial effusion may be related to malignant disease [29]. Yet, benign diseases might also be responsible of pericardial effusion. Tissue is mandatory to establish diagnosis when a malignancy is suspected. Also, some patients have concurrent pleural pathology that requires the establishment of a pleuropericardial diagnosis. From those patients with pericardial effusion, 50 % approximately present with symptoms of cardiac tamponade [29]. In these patients, pericardial decompression is mandatory for symptoms relief.

The creation of a window for drainage of the pericardium to release an accumulated effusion is effective to eliminate the physiologic effects of a cardiac tamponade. For this purpose, invasive and less invasive techniques have been proposed [29]. A percutaneous catheter drainage and balloon pericardiotomy are often performed for diagnostic and therapeutic purposes. However, recurrent or loculated effusions are best managed with a pericardial window. Surgical techniques include left lateral or anterior thoracotomy, median sternotomy, or subxiphoid pericardiotomy [29]. Thoracotomy and median sternotomy are often the subject of high morbidity rates due to pulmonary complications and are followed by long postoperative hospitalization. Subxiphoid pericardiotomy is a simple technique, yet the access to pericardium is limited. It is also associated with 10 % of relapse rates.

Thoracoscopy is an alternative to surgical pericardial or to subxiphoid drainage. It gives the possibility to explore the totality of the pleural cavity, in case of associated pleural effusion. After the phrenic nerve is identified, a stab incision was usually created on the surface of the distended pericardium using electrocautery [30]. The pericardium is then grasped with endoscopic forceps and incised with curved endoscopic scissors. Loculations and septa are broken down, and the heart is circumferentially freed with a thoracoscopic suction device. A large pericardial window is created with careful protection of the phrenic nerve. A pericardial specimen is sent for histologic and microbiologic analysis. In the event of a combined malignant pericardial and pleural effusion, talc may be applied under direct vision [30].

Thoracoscopy provides pericardial and pleural biopsies for histological diagnosis of the disease causing pericardial and pleural effusion. Drainage is achieved by the creation of a pericardial window to the pleural cavity [30]. The pleural cavity is finally drained by a chest tube. Thoracoscopy with local anesthesia has low morbidity and mortality rates in patients already with compromised cardiorespiratory system from the cardiac malfunction due to tamponade. In such patients, lateral decubitus position and single-lung ventilation might be uncomfortable [30]. General or local anesthesia with mild sedation and spontaneous ventilation have been proposed, since there are risks to such anesthesia and some operations may not require general anesthesia or intubation. The overall duration of the procedure is low not more than 45 min. However, patients with end-stage disease should undergo subxiphoid drainage only, since their survival is poor and often related to their performance status.

Conclusion

Thoracoscopy is the oldest interventional procedure in modern respiratory medicine. In one century, thoracoscopy became from a tool helping in creating therapeutic pneumothorax in patients with tuberculosis, a research tool by adding new ideas and concepts to study pathophysiological (autofluorescence) and molecular mechanisms (narrow band imaging) of pleural disorders. Its impact in the diagnosis and treatment of pleural diseases has increased over those years, yet clinical trials should define its place in the management of specific diseases such as pleural infection or pneumothorax. Despite its application in pleural diseases, thoracoscopy has also been applied in the diagnosis of lung parenchyma diseases and pericardial diseases and treatment. The further improvement of technologies will add important tools in the research, diagnosis, and treatment of disorders of the pleura.

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VATS Surgical Techniques

62

Hans Hoffmann

Video-assisted thoracic surgery (VATS) has become the diagnostic tool of choice for pleural disease, pleural effusion, interstitial lung disease, and indeterminate peripheral pulmonary nodules. In TNM staging, its role as an important adjunct has also now been well accepted. Moreover, due to the minimally invasive approach, VATS has become increasingly appreciated for the diagnosis and treatment of empyema, pneumothorax, hemothorax, chylothorax, recurrent pericardial effusion, mediastinal cysts, and mediastinal masses (Table 62.1).

In this chapter, we will give an overview of the most common applications of VATS in the diagnosis of chest diseases in the hands of the interventional pneumologist.

Anesthesia and General Surgical Technique

VATS requires general anesthesia with selective one-lung ventilation for facilitation of the procedure. This is best achieved by ventilation with a double-lumen endobronchial tube. In young children for whom no suitably sized double-lumen tube is available, a single-lumen tube with either the tip placed into the contralateral mainstem bronchus or in combination with an endoscopically placed bronchial blocker can be used. The correct placement of the double-lumen tube or the bronchial blocker should be confirmed by fiber-optic bronchoscopy. On occasion, if the patient does not tolerate single-lung ventilation (or had undergone pneumonectomy on the contralateral side), short periods of apnea after hyperventilation with FiO_2 1.0 will allow sufficient time to perform short diagnostic and therapeutic interventions. Monitoring during anesthesia is done following the standards for thoracic procedures.

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For most of the procedures (described below), the patient is positioned in the full lateral decubitus position with the operative side up and the table flexed at the patient's hip level with additional slight reverse Trendelenburg tilts (Fig. 62.1). The patient is either placed on a beanbag or secured by side positioning cushions and elevated arm support. Care should be taken that the patient's shoulder marks the highest point with the arm positioned as low as possible to allow free angulation of instruments from either direction (Fig. 62.1). The position of the surgeon depends on the procedure performed and the site of the lesion. It is recommended to approach the lesion from the same general direction with instruments and camera. The surgeon best stands facing the lesion with the camera-holding assistant on the same side and direct view on the monitor on the opposite side.

The surgical site extends from the axillary region down to the distal costal arch and from the mammary line backward to the vertebral column (Fig. 62.2). A spacious sterile draping facilitates targeted access to the entire hemithorax. Single-lung ventilation is established with the first skin incision. For most of the procedures and general inspection of the pleural space, the camera port is placed anteriorly (anterior axillary line for right-sided lesions and posterior axillary line for left-sided lesions) and low in the hemithorax (eighth intercostal space). For localized pleural effusions, it is recommended to place the first port site at the center of the fluid collection as seen on X-ray or computed tomography scans. Aspiration of fluid with a small needle may aid in localizing a fluid collection. The first incision is always made bluntly with careful digital intrathoracic exploration. After skin incision (1.5 cm), carefully dissect over the top of the rib with scissors to enter the pleural space (Fig. 62.3). Insert a finger gently to corroborate entry into the pleural space. On occasion, adhesions will be present that can be cautiously disrupted with the finger to allow safe placement of the thoracoscope (Fig. 62.4) (adopted from: SAGES manual). Additional access sites are placed under video guidance and should be positioned at a farthermost distance either cranial in the third or fourth intercostal space, if the

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Table 62.1 Common indications for diagnostic VATS

Pleural disease
Undiagnosed exudative pleural effusion
Pleural space infection and empyema thoracis
Suspected pleural malignancy/mesothelioma
Pleural mass lesions
Identification of source of hemothorax or chylothorax
Pulmonary disease
Diffuse interstitial lung disease/pulmonary infiltrates
Lung cancer: staging and assessment of operability
Indeterminate pulmonary nodules (surgical indication)
Mediastinal disease
Mediastinal cystic and solid mass lesions
Mediastinal lymphadenopathy including lung cancer staging and assessment of response to chemo-/radiotherapy
Complications of chest trauma
Hemothorax

first incision was located below the fifth intercostal space, or into the diaphragmatic recesses if the initial approach was above the fifth intercostal space (Fig. 62.5). For a diagnostic approach, two to three incisions usually are adequate; if a pulmonary wedge resection is planned, a third incision may be appropriate. For three (or more) access sites, the ports should be placed within the same 180 ° arc to allow for the comfortable "triangulation" of the instruments enabling them to target the lesion site from either side and avoid mirror image (adopted from: Yim and Sihoe 2009; SAGES manual).

The author prefers the use of a combination of minimally invasive surgery instruments (5-mm diameter) and long standard conventional instruments. The basic preference card includes a long and a short ring clamp, conventional long Metzenbaum scissors, a sponge stick, 5-mm biopsy forceps, 5-mm Metzenbaum scissors, and an electrocautery blade (Fig. 62.6). In addition, an open thoracotomy tray should always be kept ready for use in the OR in an event of bleeding. An actual trocar is only used for the thoracoscope. The 10-mm 30 ° scope is preferred for most adult procedures (5-mm scope in children). A 30 ° scope will provide optimal viewing without undue pressure on the ribs and the intercostal nerves. As described by Yim and Sihoe (2009), prewarming the thoracoscope with a sterile hot water bath effectively prevents fogging of the lens which can result from temperature differences when it is first inserted into the chest. Most working ports can be 5 mm and converted to 10–15 mm if necessary, as for stapling devices. There is a clear trend toward the use of smaller instruments and scopes, and it can be predicted that in the future, 2-mm instruments and scopes will be used as a standard in simple procedures.

Avoiding, Recognizing, and Managing Technical Complications During the Procedure

Bleeding from Chest Wall

This problem usually manifests itself as a continuous stream of blood dripping from one of the trocar sites, and/or blood seen on the surface of the pleural surfaces. Less commonly delayed presentation as a hemothorax may occur. The source of bleeding is usually the intercostal artery or in cases of lesser bleeding smaller muscular vessels. Bleeding may be controlled with a variety of techniques, including application of direct pressure, electrocautery, or in rare instances suture ligation or clipping. In rare instances, enlarging the incision facilitates identification of the bleeding source.

Injury to the Visceral Pleura

Although careful observation of the technical steps enumerated will minimize the chance of visceral pleura and lung injury, it is not a rare complication. It may occur during trocar placement or mobilization of the lung. Management depends on the size and the location of the laceration and the amount of air leakage after reexpansion of the lung. Smaller tears at the periphery of the lung with direct contact to the chest wall may not require any repair. Larger tears may be repaired by application of sealants or by open suturing through a limited anterior thoracotomy.

Insufficiency of the Stapler Line

If the thickness of the stapled lung tissue is underrated during wedge resection with the use of standard stapling devices the length of the staples will not suffice for a closure of the central part of the resection line. Furthermore, the typical congested and fragile lungs of patients with diffuse interstitial lung disease can tear easily when standard endoscopic staplers are applied. In these instances, the lung should be repaired by open suturing (3-0 monofilament tie) through a limited anterior thoracotomy performed by enlargement of one of the trocar sites.

Major Vascular Injury

Major vascular injury can occur when biopsies are taken at the hilum or mediastinum. In particular, when pressure is applied while taking the biopsy, the tip of the forceps can injure the major vessel underneath. In the event of bleeding,

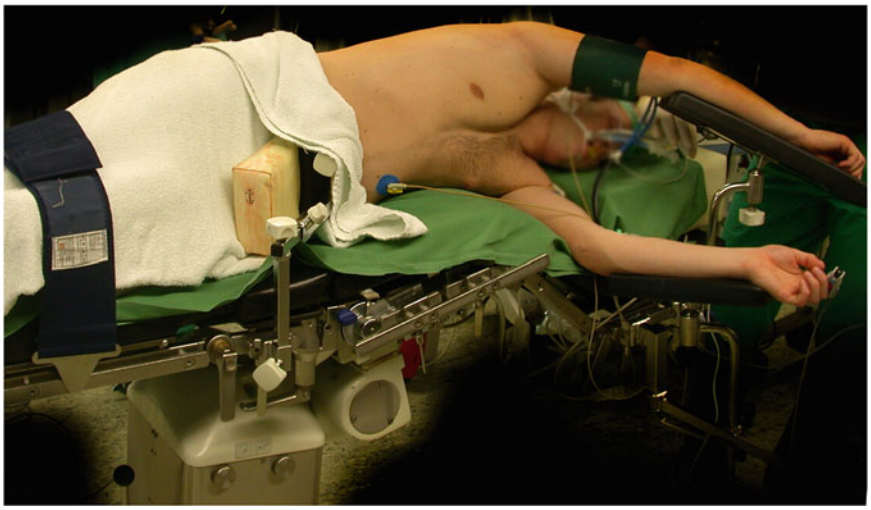

Fig. 62.1 Positioning of the patient for VATS procedures. The patient is positioned in the full lateral decubitus position with the operative side up and the table flexed at the patient's hip level with additional slight reverse Trendelenburg tilts

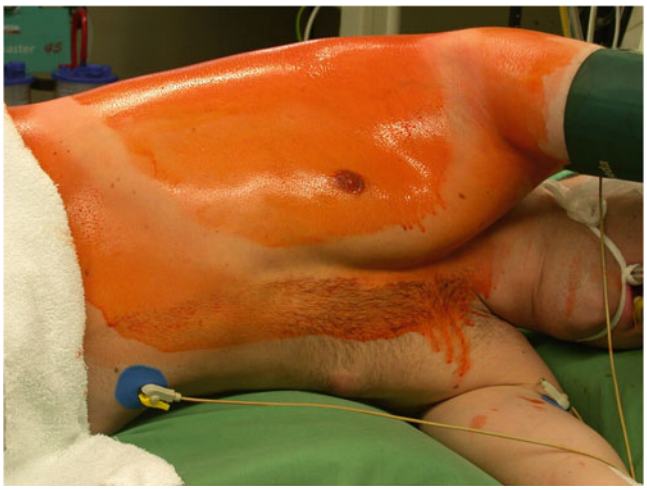

Fig. 62.2 The surgical site extends from the axillary region down to the distal costal arch and from the mammary line backward to the vertebral column

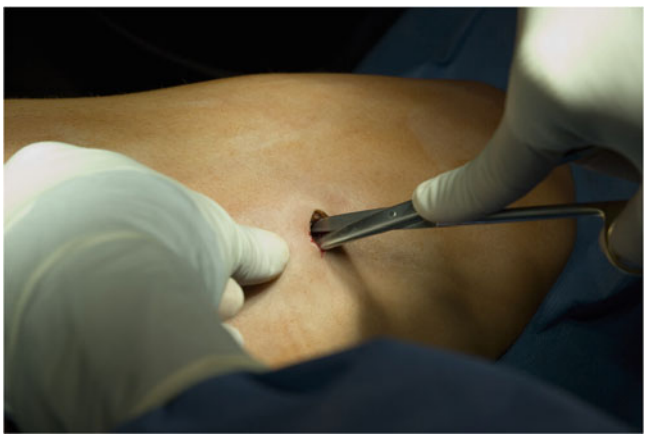

Fig. 62.3 The first incision is always made bluntly with careful digital intrathoracic exploration. After skin incision (1.5 cm), carefully dissect over the top of the rib with scissors to enter the pleural space

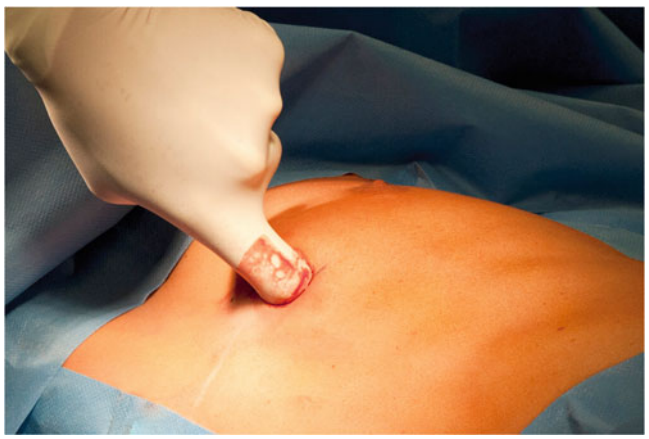

Fig. 62.4 Insert a finger gently to corroborate entry into the pleural space. On occasion, adhesions will be present that can be cautiously disrupted with the finger to allow safe placement of the thoracoscope

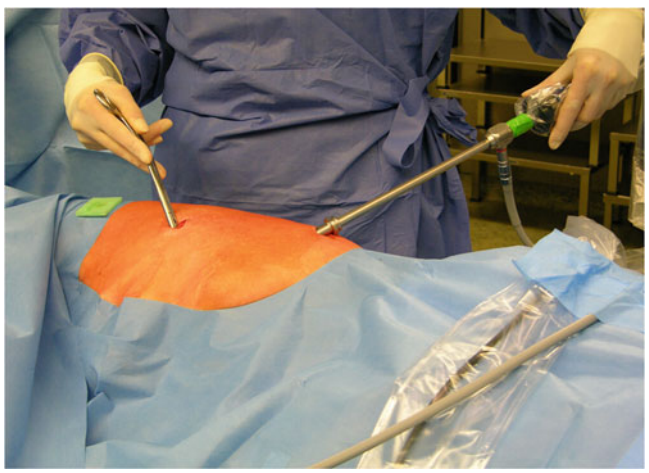

Fig. 62.5 Basic two-port VATS setting. The camera port is placed anteriorly (anterior axillary line for right-sided lesions and posterior axillary line for left-sided lesions) and low in the hemithorax (eighth intercostal space). One additional access is placed under video guidance and should be positioned in the third or fourth intercostal space

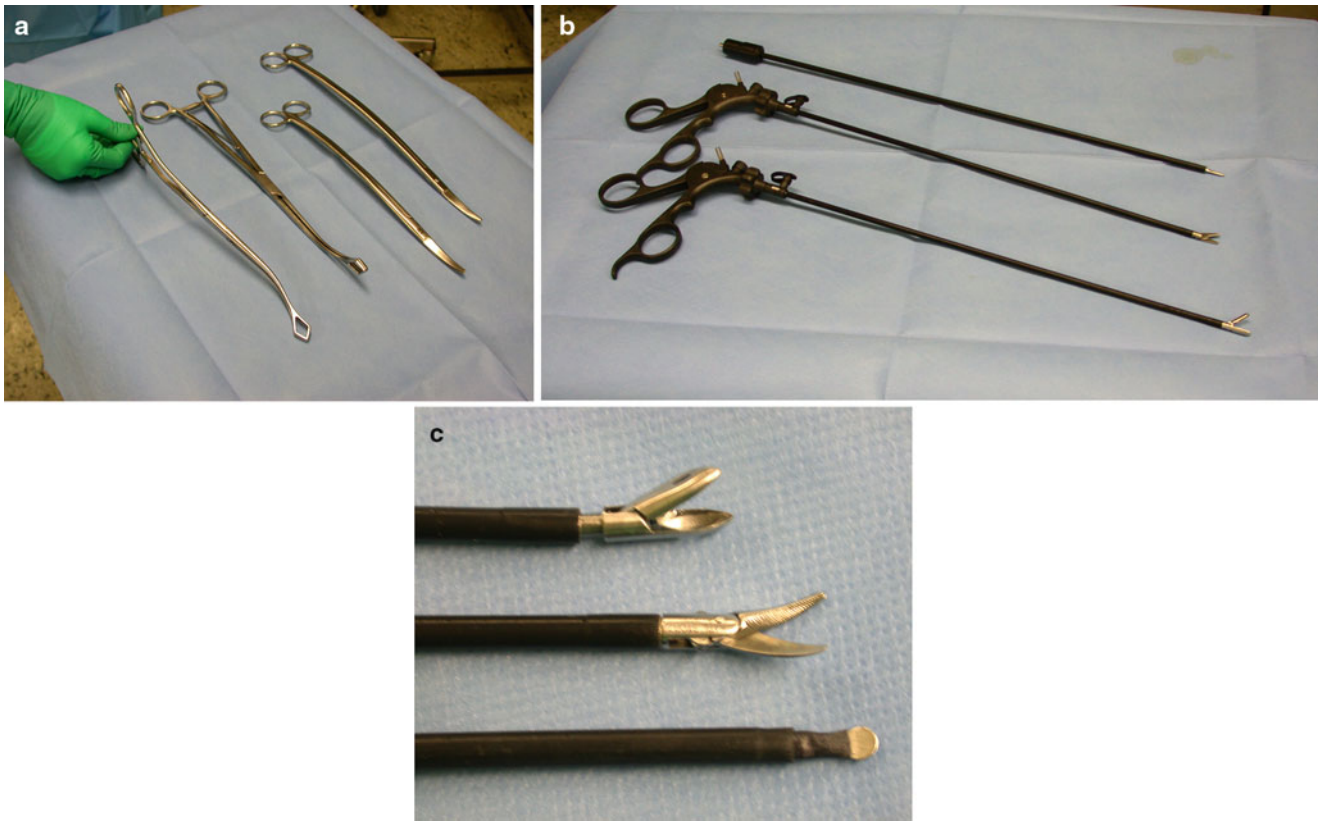

Fig. 62.6 (**a**, **b**, **c**) The basic preference card for diagnostic VATS procedures includes a long and a short ring clamp, conventional long Metzenbaum scissors, a sponge stick, 5-mm biopsy forceps, 5-mm Metzenbaum scissors, and an electrocautery blade

use the sponge stick to tamponade the bleeding. If the bleeding is not controlled by application of direct pressure, it is advisable to emergency call for assistance by an experienced thoracic surgeon and prepare for a thoracotomy.

Pleural Disease

Undiagnosed Exudative Pleural Effusions

Pleural disease, specifically pleural effusions, is one of the more common clinical problems encountered by the interventional pneumologist. Estimates of the incidence of pleural effusions vary, with some estimating an annual incidence of up to one million in the United States. The more common causes of transudative effusions are congestive heart failure and hypoalbuminemic states (e.g., cirrhosis), and those of exudative effusions are malignancy, infection (e.g., pneumonia), pulmonary embolism, and tuberculosis (adopted from: Light: The undiagnosed pleural effusion).

At most institutions, over 50% of pleural exudates seen are malignant. Although most of these patients have advanced disease with a poor prognosis, some of them may have a relatively prolonged survival. Thus, specific treatments are often justified in an attempt to effectively palliate symptoms. However, only a minority of patients with malignant pleural effusions benefit from systemic chemotherapy. Pulmonologists, therefore, find themselves in a position to treat these chronic pleural effusions, as they recur rapidly and are disabling for patients. Most patients with malignant pleural effusions (MPE) are symptomatic, and their quality of life is affected. Complaints are usually dyspnea, cough, and chest pain, and treatment is focused on relieving these symptoms. Taking into account that the tumor does often not respond to chemotherapy, adequate drainage, with or without pleural symphysis, is mandatory for such patients, and several approaches are available to provide palliation (adopted from: Rodrigez-Panadero et al. 2006).

Invasive techniques for the diagnosis of pleural effusions have gained more popularity with the advent of video-assisted technology. Thoracoscopy offers the advantages of visual evaluation of the pleura, direct tissue sampling (including lung biopsy), and therapeutic intervention (e.g., dissecting loculations and pleurodesis). VATS is indicated for diagnosing pleural effusions that have remained undiagnosed despite previous, less invasive tests (e.g., thoracentesis).

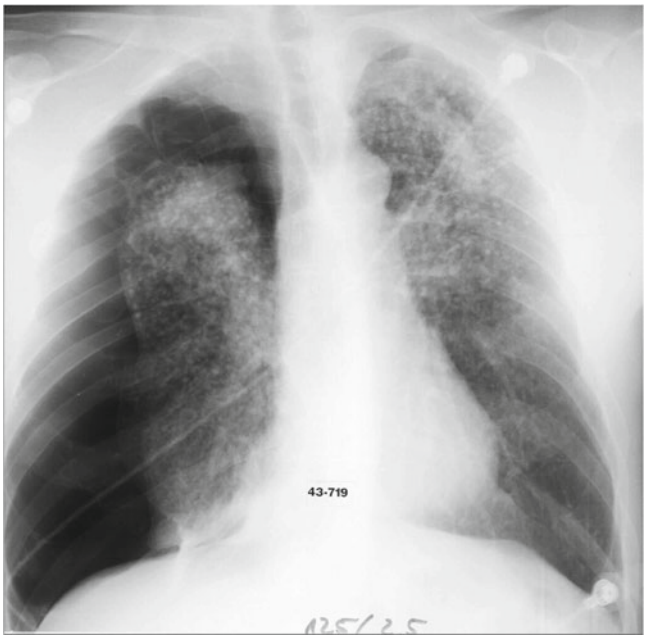

Fig. 62.7 Nonexpandable, entrapped right lung (with lymphangiosis carcinomatosa) after drainage of exudative fluid by means of an interventional (pigtail) catheter

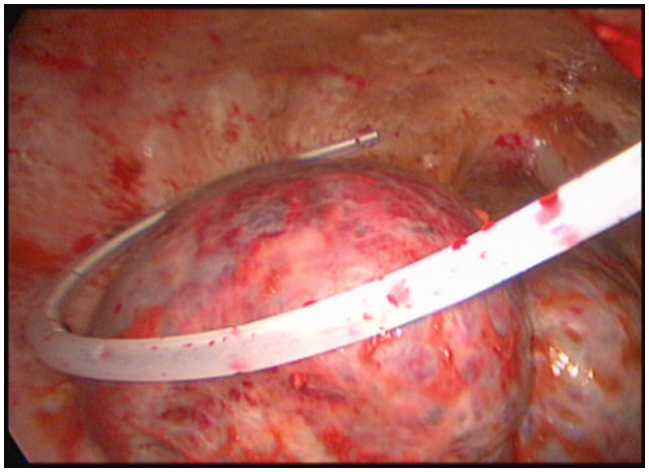

Fig. 62.8 Entrapped lung after complete drainage of fluid and insertion of a PleurX catheter. No indication for application of sclerosing agents (talc)

For the diagnosis of pleural effusions of unknown origin, the use of two ports (one for the camera, one for a biopsy forceps) is recommended as the standard approach with the surgeon to stand on the patient's front. If the patient has a chest tube already in situ, the drain site can be used as one of the access ports avoiding extra incisions.

If the patient presents with a large long-standing effusion or has undergone prior multiple thoracentesis attempts, we prefer to place a pigtail catheter 2–3 days before a scheduled VATS. This approach is recommended for three reasons: (1) dyspnea will be relieved immediately, (2) the risk of reexpansion pulmonary edema will be decreased, and (3) information is gained whether the lung is still fully expandable or partially or fully trapped. Full expansion of the lung is essential for effective pleurodesis after instillation of sclerosing agents. Among sclerosing agents available, talc (especially when applied thoracoscopically) is the most cost-effective sclerosant for the management of recurrent malignant pleural effusions. If, however, the lung is not fully expandable (Fig. 62.7), the implantation of an indwelling pleural catheter (PleurX Pleural Catheter; CareFusion, San Diego, Ca) provides a convenient, effective alternative, with good symptomatic relief following catheter placement and with few complications (Fig. 62.8). The indwelling pleural catheter can be placed under local anesthesia in the bronchoscopy suite by a single-use introduction set via J-tip guidewire and a peel-away introducer according to the manufacturer's instructions. In the VATS setting, we prefer an open approach (Fig. 62.9). Indwelling pleural catheters offer an at-home management approach which is relevant for patients with terminal malignancies. Moreover, this procedure allows (at least partial) pleurodesis in up to 50 % of the cases with a less invasive approach than chest tube placement or thoracoscopic talc poudrage.

The recommended standard VATS approach to undiagnosed exudative pleural effusions is as follows (adopted with modifications from Chap. 78, The SAGES manual):

(a) If fluid is present, aspirate and send it for culture, cytology, and chemical studies as indicated. A large trap (30–50 ml) will provide enough samples for most studies (Fig. 62.10).
(b) Perform a general inspection of all of the pleural surfaces, including the mediastinal, diaphragmatic, and visceral pleura (Fig. 62.11).
(c) Divide adhesions from the visceral to the parietal pleura with electrocoagulation shears or Metzenbaum scissors to avoid troublesome bleeding, which makes visualization more difficult (Fig. 62.12).
(d) Disrupt fluid loculations with blunt-tipped suction devices, digital manipulation, sponge stick holders, or Metzenbaum scissors. The goal is to complete and adequate visualize all of the structures and fully mobilize the lung to allow full reexpansion.
(e) Aspirate thick fluid or retained clotted hemothorax with a large-bore suction device, taking care not to injure the lung parenchyma or mediastinal structures.
(f) Take biopsy samples of any abnormal areas on the pleural or lung surfaces. Parietal pleural biopsies can be performed with endoscopic biopsy forceps or thoracoscopic graspers (Fig. 62.13a). An accepted alternative method is to circumscribe the pleural lesion with the use of a long Metzenbaum scissors and then to peel off the disk

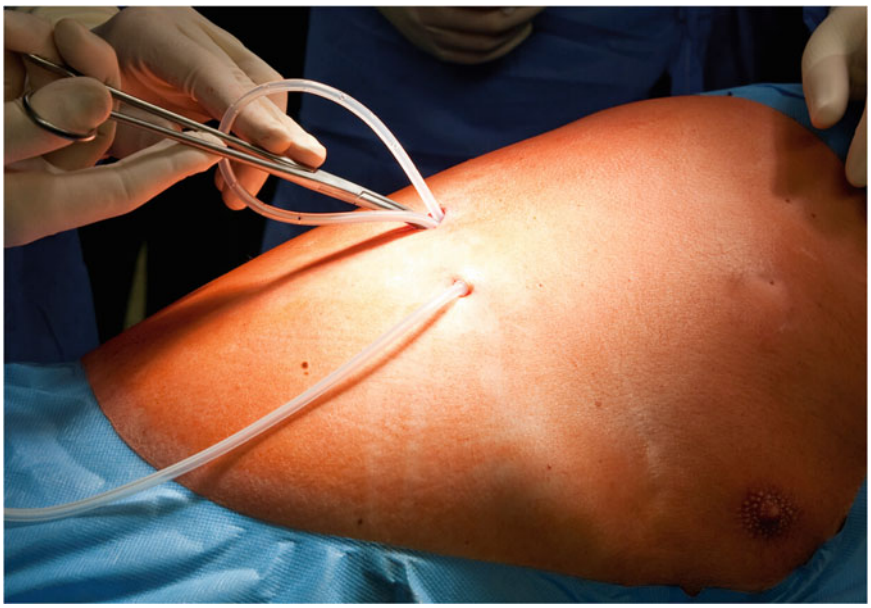

Fig. 62.9 Open approach to the insertion of a PleurX catheter. The catheter is introduced through one of the trocar sites and tunneled anteriorly

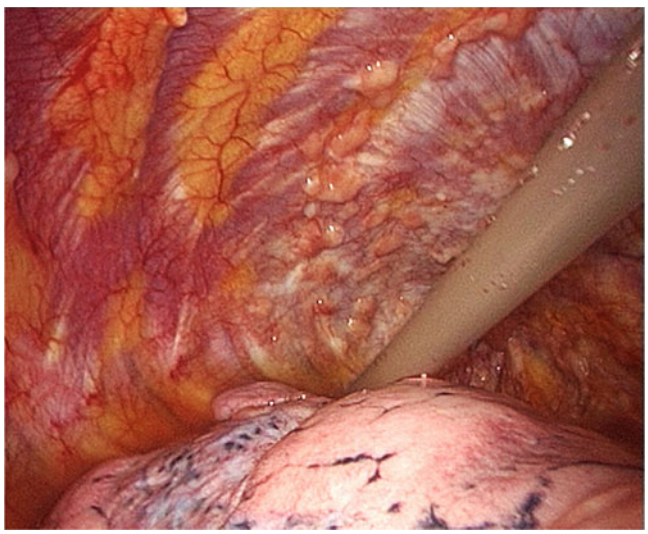

Fig. 62.10 VATS Undiagnosed exudative pleural effusions. If fluid is present, aspirate and send it for culture, cytology, and chemical studies as indicated

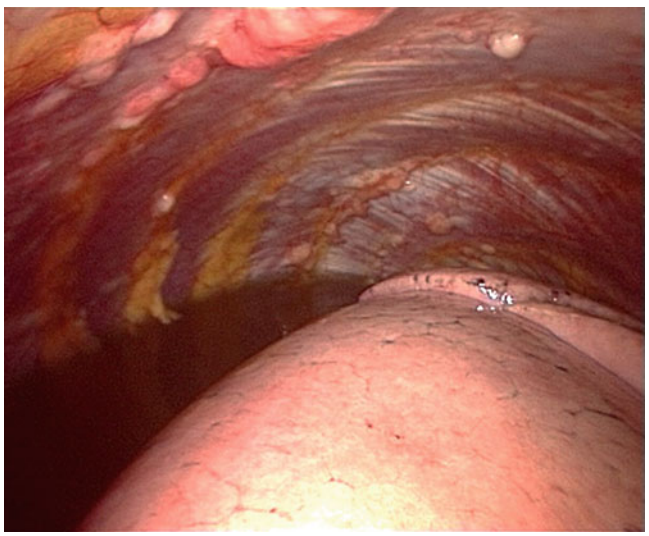

Fig. 62.11 VATS Undiagnosed exudative pleural effusions. General inspection of the pleural surfaces, including the mediastinal, diaphragmatic, and visceral pleura

of pleura, containing the lesion with a forceps (Fig. 62.13b).

(g) Use endoscopic staplers and the wedge excision biopsy technique for lung biopsies beyond the visceral pleural surface.

(h) If malignancy can be proven to be the underlying cause immediately (frozen section or undoubted macroscopic aspect) and the lung is fully expandable, then chemical pleurodesis can be achieved by insufflation of talc (3–5 g) (Fig. 62.14). In cases with a trapped lung, sclerosing agents should not be used and an indwelling catheter can be placed. If an indwelling catheter is placed, no additional chest tube is needed.

(i) At conclusion of the procedure, insert a 28-French chest tube through the inferior incision and direct it posteriorly and apically (if no indwelling catheter has been placed).

After the procedure including pleurodesis, the chest tube is connected to continuous suction (15–20 cm H_2O) for 48–72 h and removed after an additional 24 h on water seal if daily output is below 200 ml. If an air leak is present, the chest tube must remain until 24 h after resolution of the air leak.

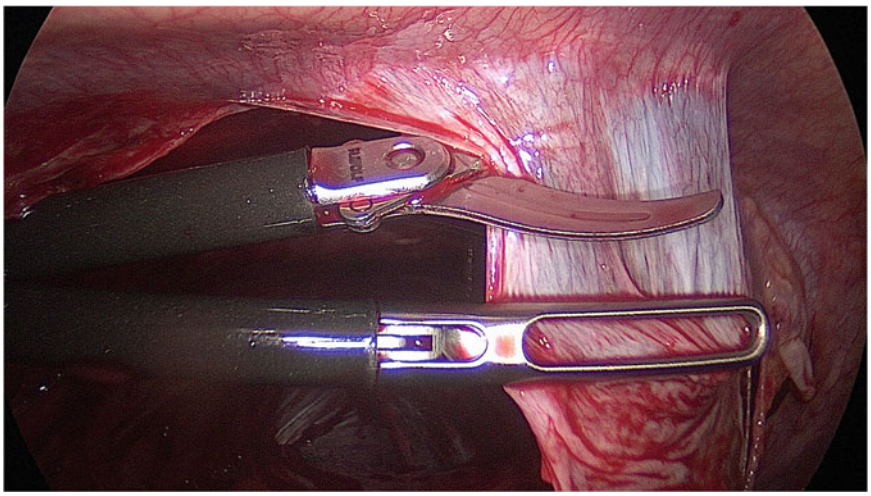

Fig. 62.12 VATS Undiagnosed exudative pleural effusions. Adhesions from the visceral to the parietal pleura are divided with electrocoagulation shears or Metzenbaum scissors

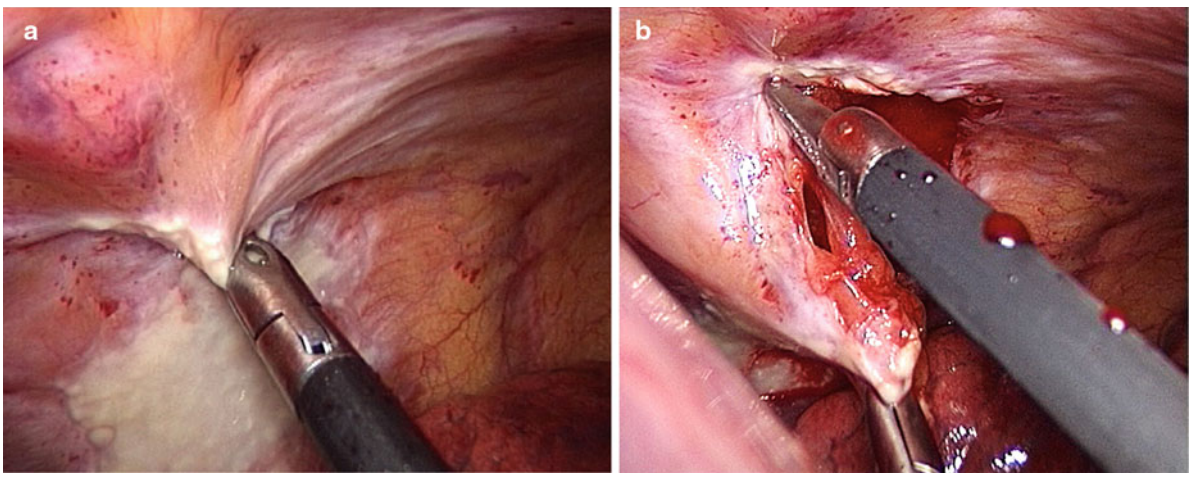

Fig. 62.13 VATS Undiagnosed exudative pleural effusions. Parietal pleural biopsies can be performed with endoscopic biopsy forceps or thoracoscopic graspers (**a**). An accepted alternative method is to circumscribe the pleural lesion with the use of a long Metzenbaum scissors and then to peel off the disk of pleura, containing the lesion with a forceps (**b**)

Pleural Space Infection and Pleural Empyema

According to the Pneumonia Outcomes Research Trial (PORT), there are three types of parapneumonic effusions: (1) uncomplicated, (2) complicated (Fig. 62.15), and (3) empyema (Fig. 62.16). Uncomplicated parapneumonic effusions are those which resolve with appropriate antibiotic therapy. Complicated parapneumonic effusions are those that do not resolve with appropriate antibiotic therapy alone, but require drainage through repeat thoracentesis or tube thoracostomy. Empyema is described as frank pus seen on thoracentesis; however, this definition has been broadened to include effusions with positive gram stain or culture. The study showed that many effusions resolved with appropriate antibiotic therapy. However, the effusions that did not resolve with antibiotics alone had a positive gram stain or culture, a significantly elevated LDH, a pH of less than 7.20, or glucose less than 60 mg/dL. These effusions require tube thoracostomy for resolution, and some require surgical intervention for complete resolution (adopted from: Dittmar: Pleural Effusions: A focus on parapneumonic effusions and from: Light: The undiagnosed pleural effusion).

Surgical intervention is a viable option but limited in patients who are poor surgical candidates or in hospital systems without available resources. Alternative therapies including the use of fibrinolytics have been evaluated in a number of clinical trials.

Maskell et al. performed a large double-blinded randomized controlled trial involving 454 patients and comparing streptokinase with placebo. This study did not show a

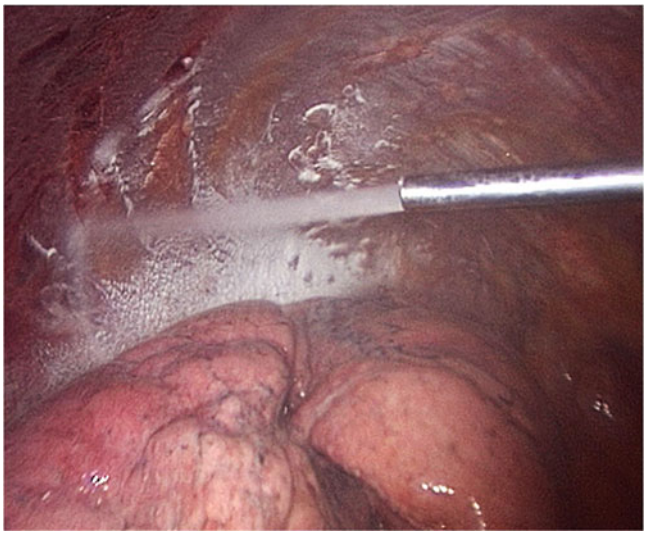

Fig. 62.14 VATS Undiagnosed exudative pleural effusions. If malignancy can be proven to be the underlying cause immediately and the lung is fully expandable, then chemical pleurodesis can be achieved by insufflation of talc (3–5 g)

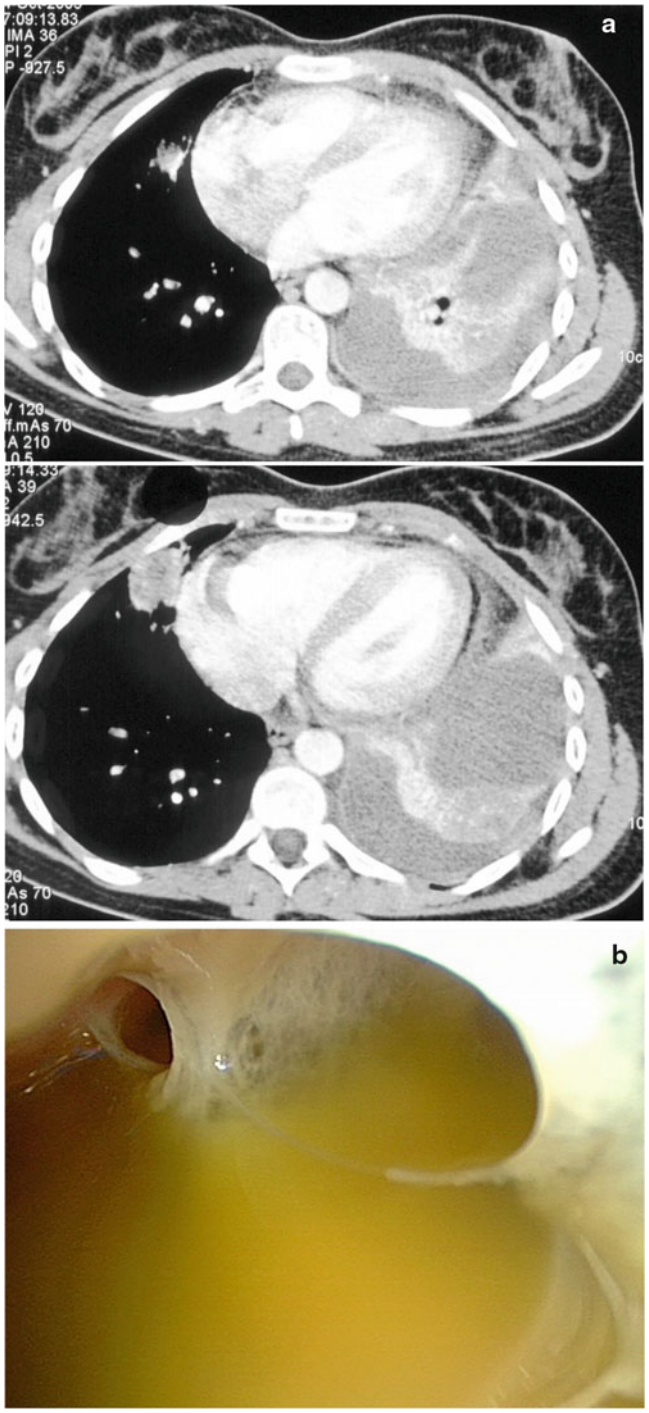

Fig. 62.15 Complicated parapneumonic effusion. (**a**) Radiologic (CT) and (**b**) intraoperative appearance, respectively

significant decrease in mortality, rate of surgery, radiographic improvement, or hospital stay. Given the large number of patients and fact that it was a double-blinded randomized control trial, the results of Maskell et al. strongly point against the use of fibrinolytics in complicated parapneumonic effusions or empyema. A follow-up meta-analysis performed by Tokuda et al. also did not support the routine use of fibrinolytics for complicated parapneumonic effusions or empyema. As such, the current recommendations for the use of fibrinolytics include poor surgical candidates and patients who do not have the resources available for surgical debridement (adopted from: Dittmar: Pleural Effusions: A focus on parapneumonic effusions).

For diagnosis and treatment of complicated parapneumonic effusions, the basic two- to three-port VATS technique described earlier is used. Because empyema is usually located dorsal/paravertebral/caudal with extension into the recessus, it is recommended for the surgeon to operate from the patient's front. VATS provides a good option for lysis of adhesions and complete drainage of a complicated parapneumonic effusion or empyema. During VATS, all loculations should be resolved, and the lung should be freed completely including dissection of the interlobar fissures (Fig. 62.17a–c). In particular, complete mobilization of the lung from the diaphragm is mandatory. Early empyema entrapping of the lung should be debrided by gently stripping off the fibrin layers and pleural peel from the surface of the visceral and parietal pleural surfaces. Care should be taken to avoid injury to the lung with potential air leaks. Entry into the appropriate plane of dissection may be facilitated by applying 10–15 cm H_2O continuous positive airway pressure (CPAP) to the operated lung. In a retrospective study, Luh et al. [5] found that early intervention by VATS resulted in better clinical results with decreased hospital stays and more rapid radiographic resolution of the effusion. VATS, however, is usually not a viable therapeutic option in late stage (organization stage) empyema. Commonly during

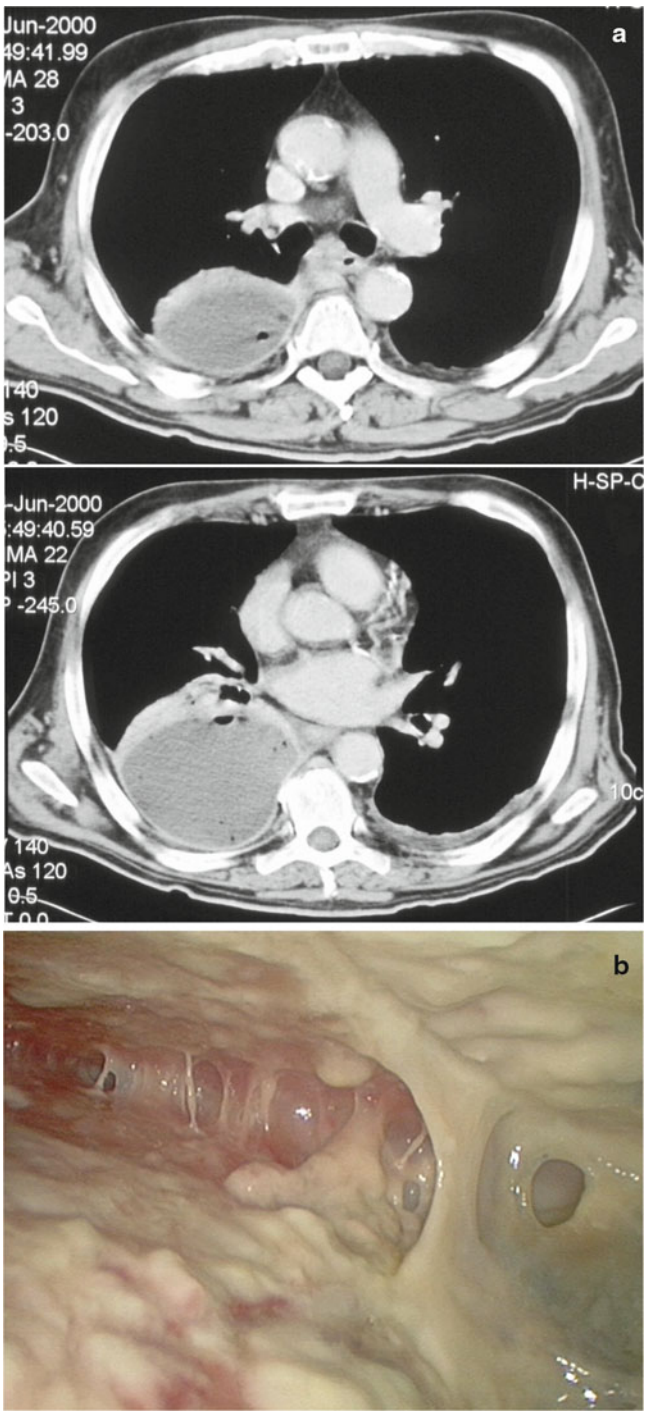

Fig. 62.16 Empyema. (**a**) Radiologic (CT) and (**b**) intraoperative appearance, respectively

this stage, surgical decortication is required with en bloc removal of all fibrous tissue from the visceral and parietal pleura to allow the lung to reexpand. This procedure is usually performed with a full thoracotomy.

Chest tubes for drainage of empyema are usually left in place for 2–4 weeks with manual rinsing procedures performed at least once daily. The chest tubes can be opened to air and connected to an open drainage system after a few days if the lung remains expanded while the chest tube is open. These tubes can later be withdrawn a few centimeters every 2–3 days until removed (adopted from: The SAGES Manual).

Mesothelioma

The histopathological diagnosis of malignant pleural mesothelioma (MPM) can be difficult because mesothelioma is a heterogeneous cancer creating various histopathological pitfalls for the reviewing pathologist. As pleural effusion is usually the first clinical sign of MPM, cytology is often the first diagnostic examination to be carried out. However, it is not recommended to make a diagnosis of mesothelioma based on cytology alone because of the high risk of diagnostic error. It is recommended that a cytological suspicion of mesothelioma is followed by tissue confirmation. Diagnosis of mesothelioma from fine needle biopsies (Abrams or Castelain needles) is associated with the same problems as cytology. A conclusive diagnosis can only be made if the material is representative of the tumor and of sufficient quantity to allow immunohistochemical characterization in the context of appropriate clinical, radiological, and/or surgical findings (adopted from: Scherpereel et al.: Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma) [11].

Thoracoscopy or VATS is the preferred diagnostic procedure in cases of suspected MPM allowing complete visual examination of the pleura, multiple, deep, and large biopsies (preferably including fat and/or muscle to assess tumor invasion) and providing a diagnosis in 90 % of cases according to the recent European guideline. The same basic two- or three-port technique described above is used. Because MPM tends to progress through port sites, as few as possible access sites should be created. The value of radiotherapy in the prevention of parietal seeding along drainage channels is questionable according to the available evidence. In a recent randomized trial conducted by O'Rourke and coworkers, prophylactic drain site radiotherapy did not reduce the incidence of tumor seeding [9].

The macroscopic aspect of mesothelioma as seen during thoracoscopy may vary during its natural history, thus it depends when the mesothelioma is first observed. As pleural mesotheliomas progress, their gross appearance becomes more suggestive of MPM, although other malignant tumors may have a pseudomesotheliomatous aspect (thymomas, carcinomas, lymphomas, angiosarcomas, etc.). According to the recent European guideline, it is recommended to take biopsies of both normal and seemingly abnormal pleura (grade 1C). It is not recommended, however, to make a

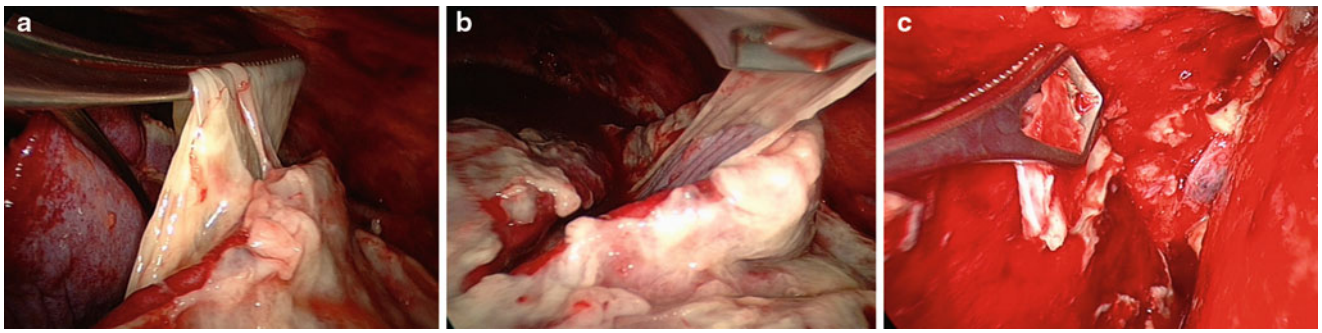

Fig. 62.17 During VATS, all loculations should be resolved, and the lung should be freed completely including dissection of the interlobar fissures, as shown in images **a** to **c**

diagnosis of MPM solely on frozen tissue sections (grade 1B). If the patient is a candidate for a combined modality treatment approach including surgery, the biopsy sites should be carefully chosen. Surgery with pleurectomy or extrapleural pneumonectomy is facilitated if the parietal pleura along the chest wall remains intact. In surgical candidates, the authors prefer to take biopsies from the diaphragm or the mediastinal pleura.

Pleurodesis is useful in patients with early stage MPM in preventing recurrent effusions. Sterile talc is preferred to other agents. Pleurodesis is most effective when performed early in the disease process, but it should not be performed before sufficient tissue for diagnosis has been obtained. In cases effusions have become loculated and/or the lung has become fixed and unable to expand fully, placement of an indwelling chest drain may occasionally be the most practical way to manage recurrent effusions in very frail patients (adopted from: Scherpereel: Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma) [11].

Pulmonary Disease

Diffuse Interstitial Lung Disease/Pulmonary Infiltrates

Diffuse pulmonary infiltrates on radiologic imaging presents a common diagnostic challenge to the pneumologist, given the wide range of possible underlying etiologies. Invasive diagnostic approaches are warranted when the clinical synthesis of the history, physical examination, laboratory data, and radiographs does not yield a confident diagnosis or the clinical course is atypical. Although bronchoalveolar lavage (BAL) or transbronchial biopsy may be diagnostic in some cases, owing to the small size of specimens obtained, diagnosis often remains elusive. BAL is often useful in the evaluation of infectious disease; however, the role of BAL is limited in other diseases such as asbestosis, IPF, UIP, nonspecific interstitial pneumonia, and sarcoidosis. Transbronchial biopsies may be diagnostic if the specimen proves granulomatous, malignant, or infectious disease. In all other instances, larger tissue specimens are warranted.

Traditionally, the diagnostic procedure of choice was the open-lung biopsy, and this approach still has its indications, as alluded by Yim and Sihoe [16]. In modern practice, however, VATS has gradually replaced open-lung biopsy in most cases by virtue of its lower morbidity, leading to reduced postoperative morbidity and pain to the patient. In addition, VATS allows for assessment of most of the ipsilateral lung, as opposed to the more limited access with an open-lung biopsy. It has also been shown in many studies (e.g., Nicols [8]) that the size and quality of the biopsy from VATS is not inferior to that obtained by the open procedure. Technically, the standard three-port approach as described above is used with the surgeon best standing on front of the patient. If the infiltrates are equally distributed on the right and left lung, it is recommended to opt for the more spacious right hemithorax. The additional lobe and fissure provide additional edges for easy biopsies. The wedge excision biopsy technique using an endoscopic stapling device is preferred. In general, two to three 45-mm staples are required for each wedge biopsy specimen. Wedge resections should be taken from two to three different sites, including areas of normal-appearing lung, as well as areas of obviously abnormal lung (Fig. 62.18 a–c). The areas should be identified by a synopsis of the radiologic (CT) diagnosis and intraoperative appearance. In addition to pathologic examination, samples should be sent for microbiology cultures. The resected specimen should be removed from the pleural space in a bag to prevent contamination of the incisions and the chest wall (Fig. 62.19).

Open-lung biopsy still has its place if the patient cannot tolerate single-lung ventilation. Open biopsy is done through a limited anterior thoracotomy. For that, single-lung ventila-

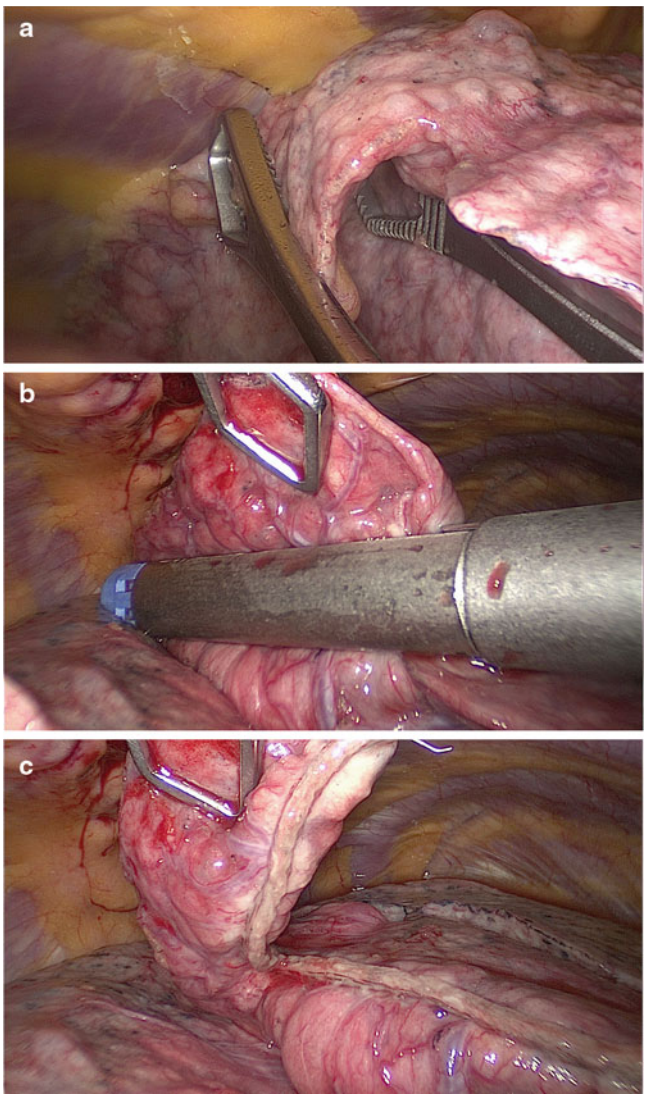

Fig. 62.18 Wedge resections should be taken from two to three different sites, including areas of normal-appearing lung, as well as areas of obviously abnormal lung (**a**); Usually, two to three 45-mm staples are required for each wedge biopsy specimen (**b**), (**c**)

tion is not generally required and the entire procedure can be performed by the bedside on the ICU if the patient is deteriorating rapidly and lung biopsy is indicated for an urgent diagnosis.

The surgeon and the pulmonologist alike have to be cognizant that any type of lung resections in patients with diffuse lung disease is associated with significant operative risks, as pointed out by Yim and Sihoe [16]. The congested and fragile lung parenchyma in these patients tears easily when standard stapling devices are used for resection. Prevention of air leakage is mandatory – however technically difficult – as these patients often present with acute respiratory failure requiring ventilatory support. At the author's institution, all operative mortality associated with lung wedge resections occurs in this group of patients.

Mediastinal Disease

Mediastinal Cystic and Solid Mass Lesions

Mediastinal masses include a wide variety of pathologies from benign lesions to extremely malignant tumors. Management strategies are highly diverse and depend strongly on the histological diagnosis as well as the extent of the disease. Operative biopsy is often warranted because less invasive approaches are limited by the small volumes of tissue obtained. In particular, mediastinal lymphoma may be difficult to diagnose accurately from the small tissue samples yielded by transthoracic needle biopsies.

In contrast to traditional surgical procedures (mediastinoscopy, anterior mediastinotomy, thoracotomy), VATS allows exploration of all mediastinal regions. It gives access to the entire hemithorax, provides larger biopsy specimens than percutaneous or endoscopic approaches, and includes also the option of a complete excision of the lesion in the same sitting. The basic two- to three-port VATS approach with the surgeon standing at the patient's back and facing the mediastinum is recommended.

Mediastinal Lymphadenopathy and Lung Cancer Staging

VATS is an excellent tool to stage mediastinal lymph nodes. Lymph nodes accessible by VATS include basically all mediastinal nodes except for highest superior nodes. As an advantage over mediastinoscopy, video-assisted thoracoscopy does allow biopsy of level five and six nodes, and it also allows access to level eight, nine, and ten (hilar) nodes. As a disadvantage compared to mediastinoscopy, thoracoscopy allows only exploration of the ipsilateral side.

Therefore, even in the ages of VATS, cervical mediastinoscopy remains the standard approach to stage superior mediastinal lymph nodes when bronchoscopic TBNA is not diagnostic. The false-negative rate of standard mediastinoscopy is generally less than 10 %, and there should be no false-positives. False-negative results are slightly higher for subcarinal nodes sampled. Mediastinoscopy has in general a low complication rate. The incidence of serious bleeding is 0.1–0.2 %. The complications of recurrent nerve injury occur slightly more frequently (0.9 %). Mortality, as reported by Specht in a series of over 11,000 mediastinoscopies compiled, was 0.15 %. The nodes accessible to standard cervical mediastinoscopy are levels 1, 2, 3, and 4 (paratracheal), level 7 (subcarinal), and sometimes level 10 (tracheobronchial angle on the right). Level 3 may be reached only in part, because the prevascular nodes may not be reached. Unapproachable by mediastinoscopy are paraesophageal

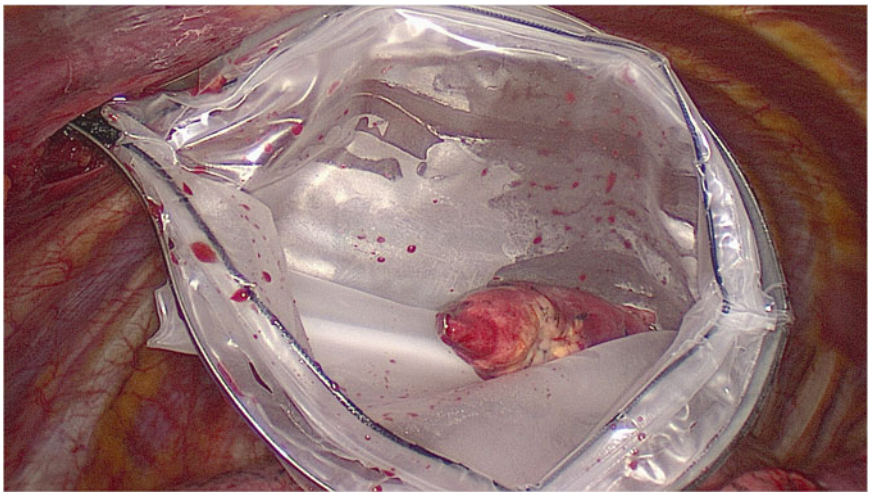

Fig. 62.19 The resected specimen should be removed from the pleural space in a bag to prevent contamination of the incisions and the chest wall

(level 8) nodes, pulmonary ligament nodes (level 9), and in general hilar (level 10) nodes and – of course – all other intrapulmonary nodes. In addition, not accessible to standard mediastinoscopy are the subaortic (aortopulmonary window, level 5) and para-aortic (level 6) nodes. Mediastinoscopy can be "extended" to evaluate also these regions. However, video-assisted thoracoscopy is a more elegant alternative to extended mediastinoscopy for the assessment of level 5 or level 6 lymph nodes.

An added benefit to using VATS to stage the mediastinum is the ability to view the tumor and to diagnose contact/compression or invasion of hilar or mediastinal structures that may not be differentiated by CT scanning, the ability to discover unsuspected pleural implants of tumor, and the ability to identify and resect synchronous satellite nodules and thus reveal causes of inoperability. Sebastian-Quetglas and coworkers conducted a study in 105 consecutive patients with lung cancer [12]. They found VATS was useful for staging T3, T4, and T doubtful clinical disease as well as N2 lesions especially for the surgical exploration of lymph nodes at the lower paratracheal level (region 4), aortopulmonary window (region 5), para-aortic (region 6), posterior subcarinal space (region 7), paraesophageal (region 8), and inferior pulmonary ligament (region 9).

Although VATS gives access to the hilar and interlobar nodes, it does not allow evaluating deeper intrapulmonary nodes that may determine N1 disease. To actually determine which lymph node position actually defines N1 disease, we analyzed a series of 292 patients diagnosed pN1 after anatomic pulmonary resection with systemic interlobar, hilar, and mediastinal lymph node dissection. Only in 13.4 % of patients positive hilar nodes (level 10) were found. In over 86 % of N1-patients, hilar nodes were negative, and N1 disease was defined by intrapulmonary lymph node involvement (level 11–14). However, Yano and associates have shown in a series of 78 patients that the survival associated with lobar N1 disease was significantly better than survival of hilar N1 disease. Therefore, although hilar involvement is only approximately 13 % in N1 disease, detection of positive hilar nodes may help identify a subgroup associated with poor prognosis.

In our experience, mediastinoscopy and videothoracoscopy complement each other to provide appropriate staging of lung cancer. Invasive staging utilizing both methods may accurately determine the presence or absence of N2 and N3 disease and identify T3 or T4 or thoracic M1 disease.

Conclusion

Video-assisted thoracic surgery (VATS) has established itself as an integral modality for the diagnosis of a variety of chest diseases. The interventional pneumologist should be familiar with the indications, opportunities, and limitations of the procedures. Realization of the procedures should be done in close cooperation with a general thoracic surgeon.

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Management Principles of Empyema

63

Anne V. Gonzalez

Introduction

Parapneumonic effusions constitute an important clinical problem. They are broadly defined as any pleural effusion secondary to pneumonia or lung abscess. Parapneumonic effusions are divided into simple parapneumonic effusions, complicated parapneumonic effusions, and empyema. This division is based on the clinical and biochemical characteristics of the pleural fluid as well as Gram stain and/or culture results. Empyema is, by definition, pus in the pleural space.

Pleural effusions develop in over 40% of patients hospitalized for bacterial pneumonia, and approximately 10% of parapneumonic effusions progress to empyema. The annual incidence of pleural infection may be up to 80,000 cases in the USA and the UK combined. Mortality is higher in patients with a parapneumonic effusion, compared with pneumonia alone. An estimated 20% of patients with empyema die.

The optimal management of parapneumonic effusions is still being defined, and this constitutes an area of active clinical research. Significant variability in the clinical approach to complicated parapneumonic effusions and empyema has been reported. This chapter reviews the management principles of complicated parapneumonic effusions and empyema in adults. Following a brief historical overview, the classification schemes designed to guide treatment decisions are presented. Key aspects of management including antimicrobial selection, chest tube drainage, use of intrapleural fibrinolytics, and surgical procedures are discussed. The specific management of pediatric empyema and posttraumatic or post-pneumonectomy empyema are beyond the scope of this chapter.

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Historical Overview

The first description of empyema treatment is attributed to Hippocrates, who in 500 BC recommended open thoracic drainage. Few advances in diagnosis or treatment would take place for over 2,000 years. Although closed drainage by underwater seal was described independently by both Hewett and Bülau in the late 1800s, open drainage remained the norm at the turn of the twentieth century. Napoleon's surgeon Dupuytren, whose name is linked to the palmar fascia contractures of liver disease, died of empyema in 1835 after declaring he would "rather die at the hands of God than of surgeons." Sir William Osler who thought "empyema needs a surgeon and 3 in. of cold steel, instead of a fool of a physician" provided a compelling description of his own empyema, before succumbing to the disease.

The influenza pandemic of 1917–1918 caused 21 million deaths worldwide. At a time when the USA had just entered World War I, influenza took a heavy toll in crowded military camps. In soldiers, the disease was frequently complicated by pneumonia due to *hemolytic streptococcus* (Group A streptococcus); this was associated with the rapid development of hemorrhagic effusions that progressed to empyema. In these patients, empyema treatment was associated with a mortality rate of 30–90%. The US Army established the Empyema Commission in 1918 in response to this deadly epidemic.

Dr. Evarts Graham, a thoracic surgeon and captain in the Army Medical Corps, was assigned to Camp Lee, Virginia. He correctly attributed the high mortality rate of hemolytic streptococcal empyema to the practice of open drainage, which resulted in pneumothorax. Dr. Graham understood the importance of negative intrapleural pressure, although it is only in 1923 that the physiologist Wirz provided detailed descriptions of negative pleural pressure and its significance to the mechanics of breathing. Empyemas traditionally treated by open drainage were associated with adhesions and pleural thickening, so that open drainage did not result in lung collapse. However, the streptokinase produced by

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DOI 10.1007/978-1-4614-4292-9_63,

Table 63.1 Light's classification of parapneumonic effusions and empyema

Class 1	Nonsignificant	Small < 10 mm thick on decubitus CXR No thoracentesis needed
Class 2	Typical parapneumonic	> 10 mm thick Glucose > 40 mg/dl, pH > 7.20 LDH < 3 x upper limit normal for serum Gram stain and culture negative
Class 3	Borderline complicated	7.0 < pH < 7.20 and/or LDH > 3 x upper limit normal and glucose > 40 mg/dl Gram stain and culture negative
Class 4	Simple complicated	pH < 7.0 or glucose < 40 mg/dl or Gram stain or culture positive Not loculated, not frank pus
Class 5	Complex complicated	pH < 7.0 and/or glucose < 40 mg/dl or Gram stain or culture positive Multiloculated
Class 6	Simple empyema	Frank pus Single locule or free flowing
Class 7	Complex empyema	Frank pus Multiple loculations

Source: From Light RW. Parapneumonic effusions and empyema. In Pleural Diseases, 5th edition 2007 (with permission)

hemolytic streptococcus may have prevented the formation of fibrinous adhesions, which allowed complete lung collapse with open thoracic drainage – particularly if performed too early in the patient's course.

The Empyema Commission advocated adequate pus drainage with a closed chest tube, avoidance of early open drainage, obliteration of the pleural space, and proper nutritional support. At Camp Lee, the mortality rate decreased to <5% when early open thoracic drainage was abandoned. The commission's recommendations have formed the basis of empyema care to this day.

Classification of Parapneumonic Effusions

The American Thoracic Society published a statement on the management of nontuberculous empyema in 1962. Three phases in the continuum of pleural infection were recognized: (1) the exudative, (2) fibrinopurulent, and (3) organizing stages.

These stages broadly correspond to the clinical evolution from simple to complicated parapneumonic effusions and frank empyema.

The first, exudative stage is characterized by the rapid outpouring of fluid into the pleural space, due to increased capillary permeability. This thin effusion has a normal glucose level (>60 mg/dl) and pH (>7.20) with no detectable bacteria and is considered a simple parapneumonic effusion. It will usually resolve spontaneously with appropriate antibiotic therapy for the underlying pneumonia.

In the absence of adequate antibiotic therapy and with ongoing inflammation within the lung parenchyma, bacterial invasion of the pleural space may occur, and the effusion then proceeds to the fibrinopurulent stage. The pleural inflammatory response is associated with depressed fibrinolytic activity, leading to fibrin deposition over the pleural surfaces and loculation of the fluid by fibrinous septae. The pleural fluid at this stage is characterized by large numbers of neutrophils, positive bacterial studies, a pH below 7.20, a glucose level below 60 mg/dl, and a rising LDH level. This is consistent with a complicated parapneumonic effusion, while frank pus is termed empyema.

A fibrinopurulent effusion that remains undrained may progress to the final organizing stage, where fibroblasts proliferate on the visceral and parietal pleural surfaces, producing a thick inelastic pleural peel. The visceral peel prevents lung re-expansion, and the persistent pleural space has the potential for ongoing pleural infection.

The stage of a parapneumonic effusion has important prognostic and therapeutic implications. Clinical characteristics alone do not allow accurate identification of patients with complicated parapneumonic effusions or empyema. Various pleural fluid parameters have been proposed to assess the stage of parapneumonic effusions and guide treatment decisions. Heffner and colleagues conducted a meta-analysis to determine the clinical utility of pleural fluid pH, glucose, and LDH measurements for identification of parapneumonic effusions requiring drainage. The authors concluded to the superior diagnostic accuracy of pleural fluid pH. However, the primary studies included in the analysis had major limitations including small sample size, lack of blinding of clinicians to the results of pleural fluid analysis, and opportunities for verification bias.

Classification schemes designed to guide therapeutic decisions reflect the progressive evolution from simple, self-resolving parapneumonic effusions to complex, multi-septated pus collections that require surgical intervention. Light's classification, summarized in Table 63.1, recognizes seven classes of parapneumonic effusions and empyema. Although it was developed to assist clinicians in the initial care of patients with parapneumonic effusions, by the author's own admission, this classification may be best suited to the stratification of research subjects.

In 2000, the American College of Chest Physicians (ACCP) published an evidence-based guideline on the medical and surgical treatment of parapneumonic effusions. The panel categorized patients with a parapneumonic effusion according to their risk for a poor outcome, and management recommendations were made accordingly. The risk for a poor outcome was established based on three criteria: pleural space anatomy, pleural fluid bacteriology, and pleural fluid

Table 63.2 Categorization of the risk of poor outcome in patients with parapneumonic effusion

	Pleural space anatomy			Pleural fluid bacteriology			Pleural fluid chemistry	Category	Risk of poor outcome	Drainage
A_0	Minimal, free-flowing effusion (< 10 mm on lateral decubitus)	AND	B_x	Culture and Gram stain results unknown	AND	C_x	pH unknown	1	Very low	No
A_1	Small to moderate free-flowing effusion (> 10 mm and < ½ hemithorax)	AND	B_0	Negative culture and Gram stain	AND	C_0	pH ≥ 7.20	2	Low	No
A_2	Large, free-flowing effusion (≥ ½ hemithorax), loculated effusion, or effusion with thickened parietal pleura	OR	B_1	Positive culture or Gram stain	OR	C_1	pH < 7.20	3	Moderate	Yes
			B_2	Pus				4	High	Yes

Source: From Colice GL, Curtis A, Deslauriers J et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. Chest. 2000;118:1158–1171 (with permission)

chemistry. In all but minimal pleural effusions (<10 mm thickness), pleural fluid analysis is necessary to adequately categorize the effusion. Four categories of risk were defined, as shown in Table 63.2, and thoracic drainage was recommended for category 3 and 4 parapneumonic effusions.

Antimicrobial Therapy

Prompt and appropriate antibiotic therapy is an essential component of the management of parapneumonic effusions and empyema. Antibiotic selection should be guided by blood and pleural fluid culture and sensitivity results, when positive. The inoculation of pleural fluid samples into blood culture bottles has been shown to increase the yield of pleural fluid cultures. Nevertheless, pleural fluid cultures remain negative in approximately 40% of complicated parapneumonic effusions.

The bacteriology of pleural infection differs from that of isolated pneumonia, and antibiotics should be selected accordingly. The microbiological data from the First Multicenter Intrapleural Sepsis Trial (MIST1) was recently published. This constitutes the largest single cohort of well-defined bacteriology in complicated parapneumonic effusions and empyema. The authors used amplification and sequencing of bacterial ribosomal RNA in addition to standard cultures. Streptococcal species, including *S pneumonia* and the *S milleri* group, were the most frequent isolates in community-acquired pleural infection, accounting for over 50% of the culture positive cases. Anaerobes were identified in 20% of community-acquired infections, and coinfection with aerobes was frequently observed. In contrast, hospital-acquired pleural infection was dominated by *Staphylococcus*, Gram-negative organisms (Enterobacteriaceae, *Pseudomonas*) and *Enterococcus* species. A quarter of the hospital-acquired isolates were methicillin-resistant *Staphylococcus aureus* (MRSA).

The MIST1 microbiological data has important implications for the empiric antibiotic selection in patients with complicated parapneumonic effusions and empyema. Antibiotic regimens for the management of community versus hospital-acquired pleural infection are proposed in Table 63.3. Anaerobic coverage is recommended for all patients with parapneumonic effusions. Adding a macrolide is unnecessary given the low prevalence of "atypical" pathogens in pleural infection. Aminoglycosides demonstrate reduced pleural space penetration and should be avoided. Evidence is lacking to guide the duration of treatment for pleural infection. Antibiotics should be continued for at least 3 weeks, and a prolonged course may be necessary.

Pleural Fluid Drainage

Pleural fluid analysis is central to the evaluation of parapneumonic effusions. Clinical characteristics cannot be used to predict which patients will require invasive procedures for resolution of the pleural infection. The estimated 10% of patients with parapneumonic effusions who require chest tube drainage must be identified and treated promptly, as a free-flowing effusion may become loculated and difficult to drain over a period of 12–24 h. The importance of timing is reflected in the adage "the sun should never set on a parapneumonic effusion."

Chest tube drainage is required in all patients with empyema, defined as purulent pleural fluid. The presence of

Table 63.3 Proposed empirical antibiotic regimens for pleural infection

	Primary regimen	Alternative regimen
Community-acquired infection		
Intravenous	Third-generation cephalosporin (cefotaxime or ceftriaxone) + clindamycin or antipseudomonal penicillin/β-lactamase inhibitor	Imipenem or meropenem
Oral	Amoxicillin/clavulanate	Clindamycin/ciprofloxacin
Hospital-acquired infection		
Intravenous	Antipseudomonal penicillin/β-lactamase inhibitor + vancomycin	Imipenem or meropenem + vancomycin

organisms on pleural fluid Gram stain or culture also warrants prompt drainage of the infected fluid. A pleural fluid pH < 7.2 is an indication for chest tube drainage in patients with suspected pleural infection. This threshold identifies a non-purulent parapneumonic effusion as "complicated." An unfavorable clinical evolution during treatment with antibiotics alone (following an initial aspiration suggestive of a simple parapneumonic effusion) should prompt patient review, repeat pleural fluid sampling, and probably chest tube drainage.

The pleural fluid pH should be measured using a blood gas analyzer and not a pH meter or pH indicator strips, which are unreliable. The pH value should be interpreted within the clinical context and if discordant repeat aspiration should be considered. In a small series of patients, variation in the pleural fluid pH was noted when separate fluid locules were sampled using ultrasound guidance.

The ACCP panel recommended thoracic drainage in all patients with parapneumonic effusions at moderate or high risk of poor outcome, based on their proposed classification. The drainage method was not specified, with therapeutic thoracentesis or tube thoracostomy being proposed as initial interventions. Beyond pleural fluid bacteriology and pH, the following features suggest thoracic drainage is necessary: large effusions, the presence of loculations, and thickened parietal pleura on contrast-enhanced CT scan. Drainage of large collections may be indicated simply for symptomatic relief, but is frequently limited by the presence of loculations. The British Thoracic Society (BTS) guidelines on the management of pleural infection in adults were recently updated, and similar indications for chest tube drainage were proposed.

An algorithm for the management of patients with parapneumonic effusions and empyema is proposed in Fig. 63.1. Pleural fluid aspiration identifies the subset of patients with parapneumonic effusions who require chest tube drainage. This initial thoracentesis may be performed with diagnostic and therapeutic intents. If all pleural fluid is removed with the initial aspiration and no fluid re-accumulates, then no further intervention may be required regardless of the fluid characteristics. Successful treatment of complicated parapneumonic effusions and empyema with serial therapeutic thoracentesis has been reported by various authors, although this approach has received relatively little consideration. No randomized controlled trial has compared serial therapeutic thoracentesis with tube thoracostomy.

No consensus exists on the chest tube size that should be used for drainage of complicated parapneumonic effusions and empyema. Large-bore chest tubes (28–36 Fr) were traditionally recommended, due to concerns that thick pleural fluid would obstruct smaller drains. However, recent data suggests that smaller pleural catheters (10–14 Fr) may be adequate in most cases of pleural infection and are better tolerated by patients. No randomized trial has compared small versus large-bore chest tubes for the management of pleural infection. A subgroup analysis of the MIST1 trial showed no difference in efficacy between large-bore and small-bore drains. The smaller chest tubes should be managed with regular saline irrigation to maintain catheter patency. The application of suction (−20 cm H_2O) may improve drainage and is frequently employed.

Accurate catheter placement may be more important to successful pleural fluid drainage than chest tube size. The BTS guidelines recommend that chest tube insertion be performed under image guidance whenever possible. The PA and lateral chest radiographs may be the first investigation to suggest the presence of a pleural effusion, but thoracic ultrasound allows exact localization of the fluid. Ultrasound can detect small amounts of pleural fluid and identify fluid septations (Fig. 63.2). Ultrasound guidance for pleural procedures is expected to become standard of care, as it improves the safety and accuracy of the initial thoracentesis, and can guide chest tube placement.

Clinical and radiographic improvement should be observed within 24 h of successful chest tube drainage. Poor clinical progress may be due to incomplete fluid drainage or inadequate antibiotic coverage. In this context, culture results should be reviewed, and a CT scan of the chest obtained to delineate the infected pleural space. Contrast-enhanced CT scan (performed in the tissue phase) will identify visceral pleural thickening, pleural fluid loculations, and the chest tube position (Fig. 63.3). Significant residual fluid collections may be amenable to drainage with additional chest tubes, inserted under image guidance. In contrast, proceeding directly to VATS with lysis of adhesions should be considered in the presence of multiple fluid locules.

Chest tube removal is appropriate once imaging confirms successful pleural fluid drainage, and the clinical evolution is consistent with resolution of pleural sepsis. Chest tubes are generally left in place until the volume of drainage decreases to less than 50 ml per 24 h. A chest tube that ceases to func-

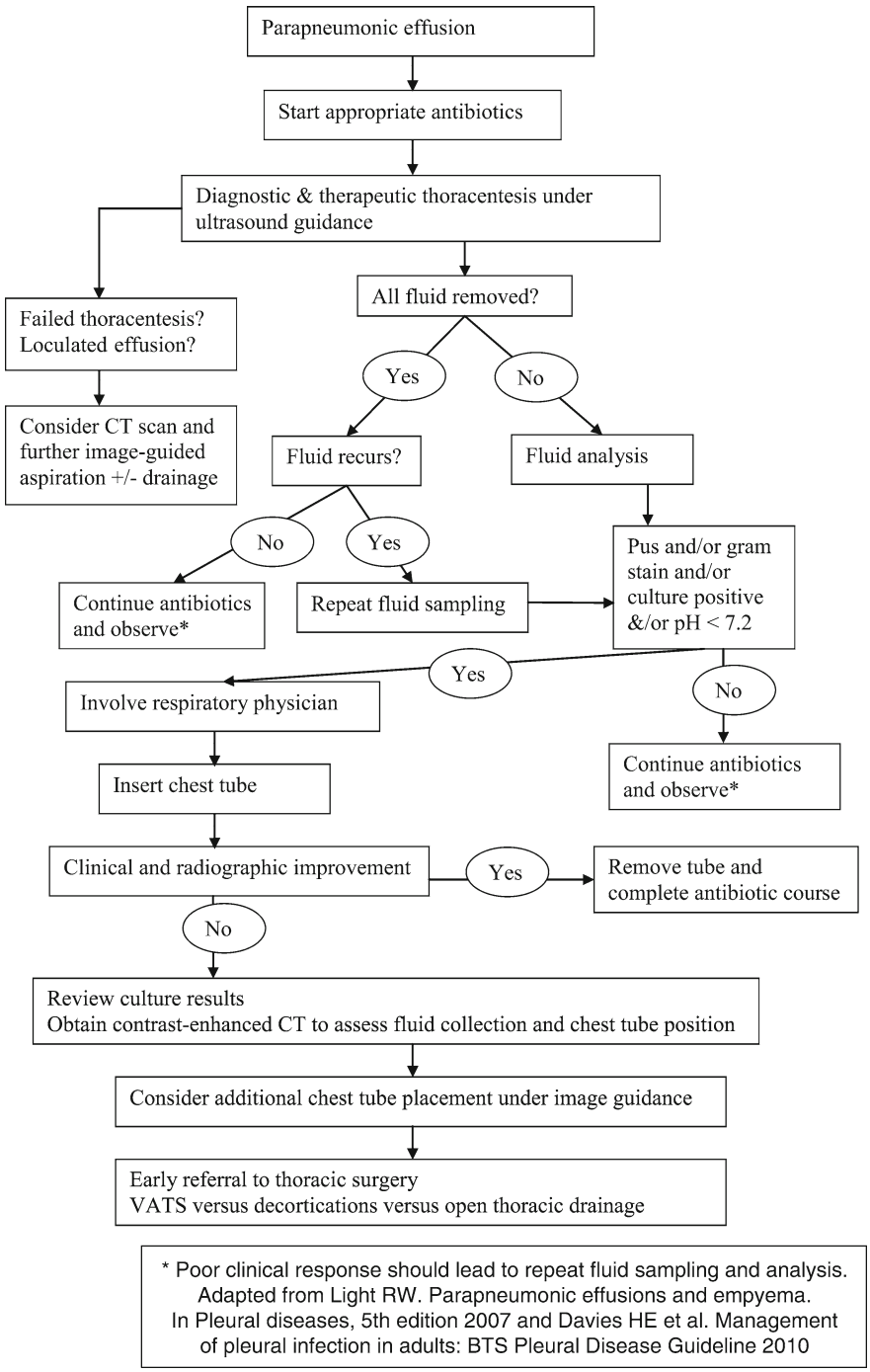

Fig. 63.1 Algorithm for the management of patients with parapneumonic effusions and empyema (adapted from RLight chapter and BTS 2010 guideline)

tion should be promptly removed, as it then simply becomes a conduit for infection.

Specialist Referral and General Medical Care

A respiratory physician should be involved in the care of any patient who requires chest tube drainage. Involvement of thoracic surgery when the patient does not respond to initial drainage is recommended. Delayed specialist referral of patients with pleural infection has been identified as a factor that is associated with increased morbidity.

Adequate nutritional support was advocated by the Empyema Commission of 1918. This aspect of patient care should not be neglected. Hypoalbuminemia has been found to correlate with mortality in patients hospitalized for empyema.

Finally, thrombosis prophylaxis should proceed according to current recommendations. The most recent ACCP guidelines on the prevention of venous thromboembolism (8th edition) recommend prophylaxis with low molecular

weight heparin or low-dose unfractionated heparin in the absence of any contraindications.

Predictors of Clinical Outcome

Patients with complicated parapneumonic effusions may require invasive surgical procedures for resolution of the pleural infection. Though early identification of the subset of patients who will fail initial management with antibiotics and tube thoracostomy would be very helpful, attempts at finding predictors of outcome in patients with complicated parapneumonic effusions and empyema have been disappointing.

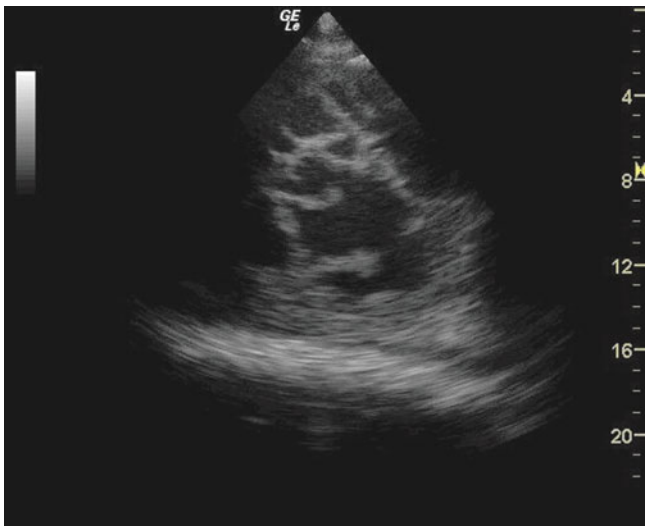

Fig. 63.2 Ultrasound appearance of a multiloculated empyema. Multiple septations and thickening of the visceral pleura are visualized

A retrospective review of patients with complicated parapneumonic effusion or empyema identified loculation and (counterintuitively) low pleural fluid leukocyte count as independent predictors of failure of tube thoracostomy. CT and ultrasound have established roles in the investigation of parapneumonic effusions and facilitate pleural fluid drainage. Kearney et al. questioned whether ultrasound (fluid hyperechogenicity, septations) or CT features (pleural thickening, thickening of extrapleural fat) would predict the effusion stage or need for surgical treatment. Unfortunately, neither technique reliably identified the patients who subsequently required surgical intervention.

Davies and colleagues examined clinical predictors in 85 consecutive patients with pleural infection managed with antibiotics, chest tube drainage, and intrapleural fibrinolytics. In this prospective study, pleural fluid purulence was observed more frequently in the patients who failed medical treatment but had a low positive predictive value for medical failure. In the subsequent MIST1 trial, neither pleural fluid purulence nor fluid loculations were associated with a poor outcome.

Intrapleural Fibrinolytics

The use of intrapleural fibrinolysis in patients with empyema was first reported in 1949. Tillet and Sherry injected streptococcal fibrinolysin (streptokinase) into the pleural cavity of patients with "fibrinous, purulent and sanguinous pleural exudations." Administration of streptokinase resulted in demonstrable intrapleural fibrinolytic activity and facilitated pleural drainage in patients with empyema and hemothorax. However, the partially purified preparation was associated with immunological adverse effects, and its use failed to enter routine clinical practice.

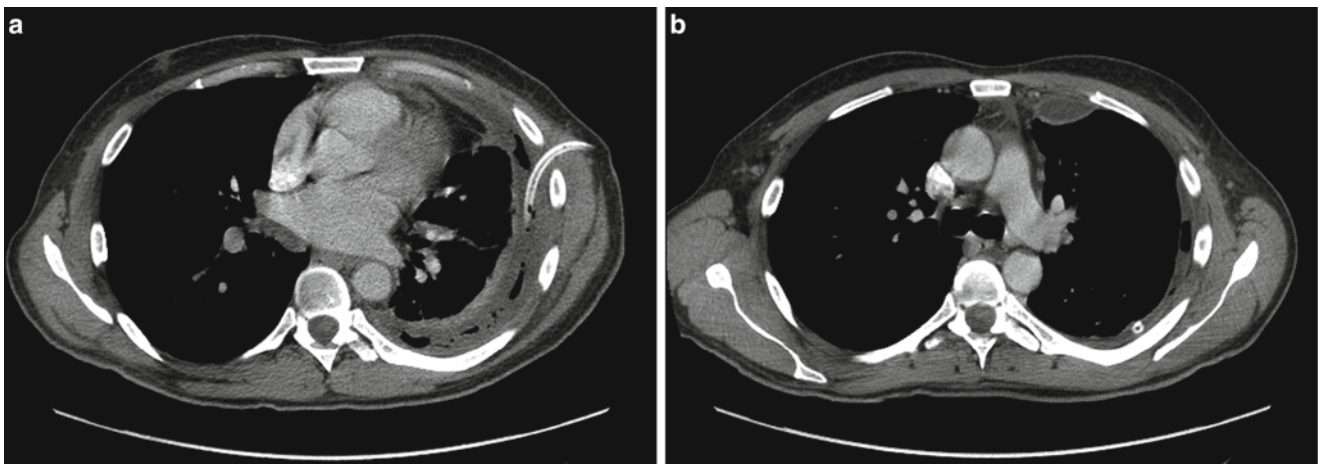

Fig. 63.3 Contrast-enhanced CT scan images of an empyema, following initial insertion of a 16-Fr chest tube by Seldinger technique (**a**). There is thickening and enhancement of both the visceral and parietal pleural surfaces (split-pleura sign, **b**)

Table 63.4 Randomized, placebo-controlled trials of intrapleural fibrinolytics in adult empyema

Author year	Number of patients	Study design	Intervention	Outcome
Davies et al. (1997)	24	Randomized controlled trial Double-blind	Streptokinase 250,000 IU daily versus saline × 3 days	Greater volume of pleural fluid drained and greater radiographic improvement with SK No significant difference in need for surgery
Bouros et al. (1999)	31	Randomized controlled trial Double-blind	Urokinase 100,000 IU daily versus saline × 3 days	Shorter time to defervescence, greater volume of pleural fluid drained, and greater radiographic improvement with UK Shorter length of hospitalization with UK
Tuncozgur et al. (2001)	49	Randomized controlled trial	Urokinase 100,000 IU daily versus saline × 5 days	Shorter time to defervescence, greater volume of pleural fluid drained, and shorter hospitalization with UK Lower decortication rate with UK – but one criteria for surgery referral was lack of radiographic improvement
Talib et al. (2003)	24	Randomized controlled trial	Streptokinase 250,000 IU daily versus saline × 6 days	Greater volume of pleural fluid drained and greater radiographic improvement with SK Shorter duration of chest tube drainage with SK
Diacon et al. (2004)	44	Randomized controlled trial Double-blind	Streptokinase 250,000 IU daily versus saline for up to 7 days	Higher clinical success rate (control of infection, adequate drainage, and radiographic clearance) with SK after 7 days Fewer referrals to surgery with SK – but one criteria for surgery referral was lack of radiographic improvement
Maskell et al. (2005)	430	Randomized controlled trial Double-blind	Streptokinase 250,000 IU BID versus saline × 3 days	No significant difference in the proportion of patients who died or needed surgical drainage at 3 months No benefit of SK in terms of mortality, rate of surgery, radiographic outcomes, or length of hospitalization

Interest in the use of intrapleural streptokinase resurged in the late 1970s. Early case series suggested a beneficial effect of intrapleural fibrinolytics in patients with empyema and complicated parapneumonic effusions. Small controlled and randomized studies also supported a role for intrapleural fibrinolytics. The limitations of uncontrolled observational studies are well known. In addition, many observational and controlled studies used pleural fluid drainage volume as a principal endpoint. This is problematic because streptokinase administration leads to increased pleural fluid production, as was demonstrated by Strange et al. in an animal model of empyema. The controlled study of Chin and Lim demonstrated no correlation between increased pleural fluid drainage after streptokinase administration and reduced morbidity.

The results of randomized, placebo-controlled trials of intrapleural fibrinolytics in adult empyema are summarized in Table 63.4. Recent randomized, placebo-controlled trials have cast doubt on the role of intrapleural streptokinase in the management of complicated parapneumonic effusions and empyema.

Diacon and colleagues conducted a single-center, double-blind, randomized placebo-controlled trial of intrapleural streptokinase for empyema and complicated parapneumonic effusions. A total of 53 patients were randomized to streptokinase versus saline following ultrasound-guided placement of 24- or 28-Fr chest tubes. Rinse therapy was continued daily for up to 7 days or until drainage was less than 100 ml per day. Nine patients were excluded for various reasons. Clinical treatment success and need for surgery were the main outcome measures. Patients were referred to surgery for ongoing sepsis with a significant residual pleural collection or lack of satisfactory clinical or radiological improvement beyond 7 days.

No difference in outcomes was observed at 3 days. After 7 days, a higher clinical success rate and fewer referrals to surgery were observed in the streptokinase-treated group (9% versus 45%, $p=0.02$). The positive study results have come into question due to the high failure rate observed in the control group; this has been attributed to the criteria used for surgical referral. Indeed, the indication to proceed with surgery for lack of radiographic improvement is questionable. The single-center study was also underpowered to assess differences in mortality.

The First Multicenter Intrapleural Sepsis Trial (MIST1) study results were reported in 2005. In this double-blind trial, 454 patients with empyema or complicated parapneumonic effusions were randomized to intrapleural streptokinase (250,000 units BID × 3 days) versus placebo. The primary outcome was the number of patients who died or required surgical drainage during the 3 months after randomization. The need for surgical drainage was determined by bedside clinicians based on a substantial residual pleural collection and persistent infection. Chest tube size and placement, and

antibiotic selection were left to the treating physician. The main analysis included 430 subjects.

There was no significant difference between the two groups in the proportion of patients who died or needed surgery. A trend toward increased adverse effects was observed in the streptokinase group (chest pain, fever, or allergy), but no excess of local or systematic hemorrhage was reported.

A meta-analysis of all randomized trials comparing fibrinolytics agents with placebo that included the MIST1 trial data did not support the routine use of fibrinolytics therapy for patients with parapneumonic effusions who require chest tube drainage. A Cochrane database review published in 2004 concluded that intrapleural fibrinolytics were beneficial in the treatment of patients with empyema and complicated parapneumonic effusions, but that further randomized controlled studies were needed.

The Cochrane review update published in 2008 was based on seven randomized controlled trials with 761 patients. Treatment failure was defined as death or the need for surgery. Intrapleural fibrinolytics did not reduce the risk of death, but reduced the need for surgical intervention (RR 0.63, 95% CI 0.46–0.85). However, significant discordance was observed between earlier positive studies and the negative MIST1 trial.

The ACCP guideline published in 2000 suggested that chest tube drainage may be insufficient for a large proportion of patient with category 3 and 4 parapneumonic effusions and recommended the use of intrapleural fibrinolytics. Use of intrapleural fibrinolytics was also included in the 2003 BTS guidelines for the management of pleural infection. In light of recent data, the 2010 BTS guidelines state that there is no indication for the routine use of fibrinolytics in patients with pleural infection.

There may be a subgroup of patients with loculated complicated parapneumonic effusions and empyema who benefit from intrapleural fibrinolytics. In the 2008 Cochrane review of Cameron et al. fibrinolytics reduced overall treatment failure (death or need for surgery) in the subgroup of patients with proven loculations, but this conclusion was limited by the methodological flaws of one study. One clinical situation where intrapleural fibrinolytics may have a role is the management of a large effusion that is resistant to initial chest tube drainage and causes significant symptoms. Patients who do receive intrapleural streptokinase develop systemic antibodies and should be given a streptokinase exposure card. For this reason, streptokinase is not available for intrapleural administration in the USA.

Recently, there has been interest in the use of the more potent fibrinolytic agent tPA (tissue plasminogen activator), the activity of which is not limited by endogenous plasminogen levels as is the case for streptokinase. Small series have reported success with the use of intrapleural tPA, and a recent randomized study has examined the combination of intrapleural tPA and DNase in pleural infection.

Intrapleural DNAse

In their 1949 paper, Tillet and Sherry used a combination of streptokinase and streptococcal desoxyribonuclease (streptodornase). Rapid lysis of pus nucleoproteins by deoxyribonuclease was noted, with a marked fall in the viscosity of purulent pleural fluid. Streptokinase does not reduce the viscosity of infected pleural fluid, but simply disrupts the fibrinous septations between various pockets of pus. Reducing the viscosity of pleural fluid may facilitate fluid drainage and improve patient outcomes.

The combination of streptokinase and streptodornase (Varidase) has been shown to liquefy the thick purulent material isolated from a rabbit empyema model. Deoxyribonuclease (DNase) has been shown to significantly reduce the viscosity of human empyema fluid in vitro. In a rabbit model of empyema, the combination of recombinant tPA and DNase was significantly more effective than either agent alone. DNase is already used in patients with cystic fibrosis to reduce sputum viscosity. Simpson and colleagues reported the successful use of DNase in a patient with empyema who had failed chest tube drainage with intrapleural streptokinase.

MIST2 is a double-blind, placebo-controlled, 2×2 factorial trial designed to examine the role of intrapleural tPA and DNase in patients with pleural infection. Two hundred and ten patients were randomly assigned to one of four intrapleural treatments for 3 days: tPA, DNase, tPA and DNase or double placebo. The combination of intrapleural tPA and DNase resulted in a greater decrease in radiographic pleural opacity than placebo. No pleural drainage benefit was seen with either tPA of DNase alone. Combined tPA and DNase was associated with a reduction in the frequency of surgical referral at 3 months, and a reduction in mean length of hospital stay. Mortality and frequency of serious adverse events were similar among the four treatment groups.

Surgical Intervention

Surgical intervention may be required in up to 30% of patients with complicated parapneumonic effusions or empyema. Unfortunately, as mentioned earlier, no clinical predictor can reliably identify the patients who will require surgical intervention. Surgical referral should be considered in patients with ongoing sepsis and a persistent pleural fluid collection, despite appropriate antibiotics and chest tube drainage. The BTS guidelines recommend that a surgical opinion be sought within 5–7 days of failed medical treatment. A definitive procedure should be performed within 14 days of initial presentation.

The options for surgical management of complicated parapneumonic effusions and empyema include video-assisted thoracoscopic surgery (VATS), thoracotomy with decortication, and open thoracic drainage.

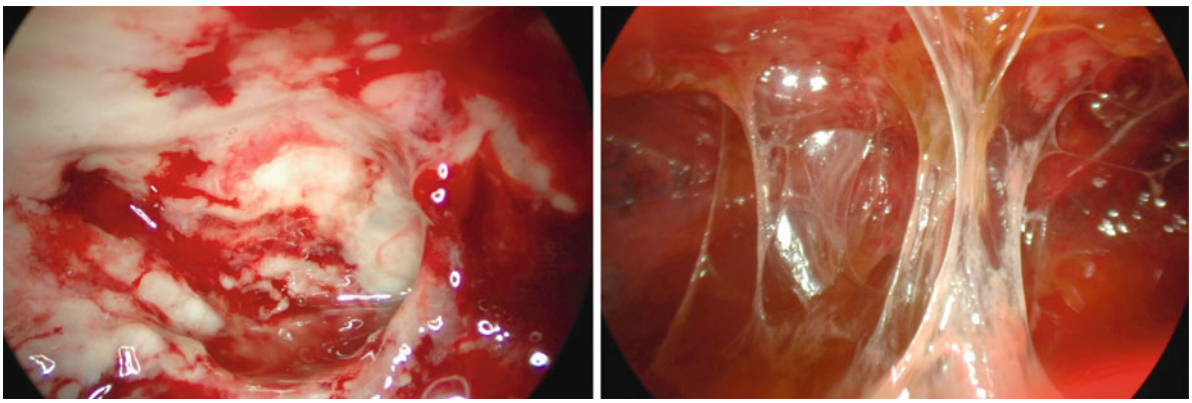

Fig. 63.4 Medical thoracoscopy images of an empyema, demonstrating pus (**a**) and multiple adhesions (**b**) (The photos are a courtesy of Drs. Gian Pietro Marchetti and Gian Franco Tassi, Spedali Civili di Brescia, Brescia, Italy)

VATS was introduced in the late 1980s. VATS offers an effective approach to the incompletely drained, loculated parapneumonic effusion and is less invasive than thoracotomy with decortication. It is associated with less patient discomfort and shorter hospital lengths of stay. A retrospective series of 234 patients who underwent VATS for complicated parapneumonic effusions and empyema was published by Luh and colleagues. VATS was the only surgical intervention required in 194 patients (83%). The authors reported a 10% conversion rate to open thoracotomy.

Two small randomized trials have compared VATS with medical therapy. Wait et al. randomized 20 patients with empyema to chest tube drainage with intrapleural streptokinase versus VATS. The VATS group had a significantly higher treatment success rate (10/11 versus 4/9, $p<0.05$). The VATS approach was associated with lower chest tube duration and a shorter length of stay. However, the main criterion for treatment failure was inadequate drainage on chest radiograph, and the positive result of the trial is due to the high failure rate in the medical treatment group. The lack of blinding may have also affected the assessment of outcomes.

Bilgin et al. randomized 70 patients with empyema to VATS versus tube thoracostomy. A significantly lower proportion of patients who underwent VATS required open decortication (17% versus 37%, $p<0.05$), and the average length of stay was also lower in the VATS group (8 versus 13 days). However, the decisions to proceed with surgical treatment were unblinded and were mainly based on the results of imaging (pleural thickening, loculated empyema). Further data are required to clarify the indications and timing of VATS in the management of empyema.

There has been increasing interest in the use of medical thoracoscopy for patients with pleural infection. Medical thoracoscopy refers to video-assisted thoracoscopy performed under local anesthesia and sedation by a chest physician. It has a well-established role in the diagnosis and management of malignant pleural effusions and may have a role in the lysis of fibrinous adhesions for multiloculated parapneumonic effusions, followed by judicious chest tube placement.

Brutsche and colleagues reported a retrospective multicenter series of 127 patients who underwent medical thoracoscopy in the treatment of multiloculated empyema or complicated parapneumonic effusions (Fig. 63.4). The presence of multiple loculations was established by chest ultrasonography. Medical thoracoscopy with chest tube placement was the only intervention performed in 91% of patients. Overall, 94% of patients avoided surgery. Despite having selected a group of patients with evidence of loculations on ultrasound, the rate of surgery was much lower than in the MIST1 trial, where 29% of patients were referred for VATS or thoracotomy. Further studies are needed to clarify the role of medical thoracoscopy in the management of empyema.

Decortication refers to the removal of fibrous tissue from the visceral and parietal pleura and evacuation of pus from the pleural cavity. This is usually performed via an open thoracotomy (Fig. 63.5). Decortication is a major surgical procedure with a mortality of approximately 10%. The only indication for decortication in the first few weeks of empyema treatment is control of the infection and not impairment of lung function. With adequate control of the pleural infection, even thick pleural peels may resolve gradually and lung function can return to normal. Decortication for persistent lung function impairment should be delayed for several months after the initial infection.

In patients too debilitated to undergo decortication, open thoracic drainage may be considered. Although usually performed under general anesthesia, local anesthesia may be used. The Eloesser flap consists in the creation of a skin-lined fistula for open drainage, following resection of a rib segment in the lowest part of the empyema cavity.

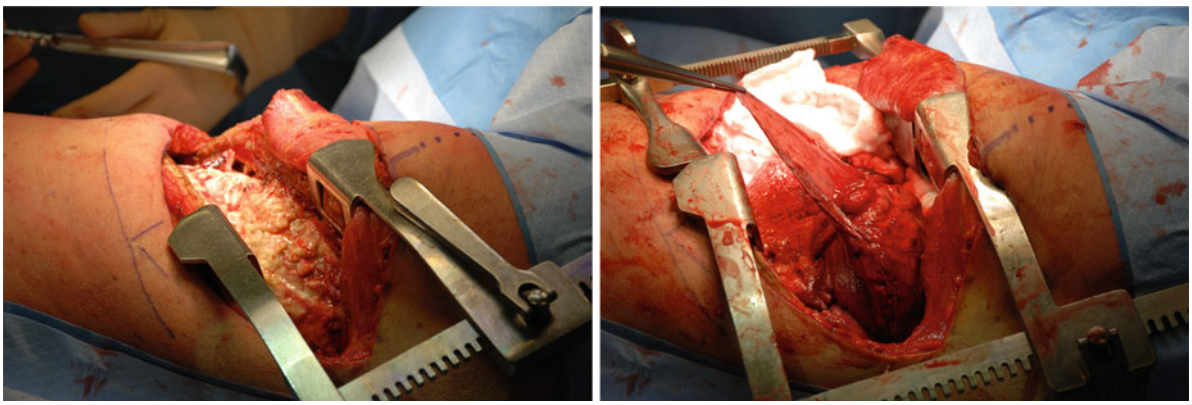

Fig. 63.5 Open decortication for empyema. The empyema cavity with pus and adhesions (**a**) and visceral pleural peel being removed from the lung surface (**b**) are shown (The photos are a courtesy of Dr. Christian Sirois, McGill University Health Centre, Montreal, Canada)

The Clagett window achieves open drainage through resection of two or three rib segments over the most dependent portion of the empyema cavity, followed by lining of the window with musculocutaneous flaps. Open thoracic drainage has the potential to control life-threatening pleural infection in frail patients. It should not be performed too early in the patient's course, as open drainage before sufficient inflammatory adhesions between visceral and parietal pleura have been created would result in pneumothorax. Patients and their family should be aware of the prolonged period of open drainage that will be required (median 3–4 months) before obliteration of the empyema cavity occurs.

Conclusion

Recommendations for the management of complicated parapneumonic effusions and empyema are limited by the incomplete availability of data derived from prospective, randomized controlled trials. The therapeutic principle adopted by Celsus "ubi pus, ibi evacua" – where there is pus, (there) evacuate it – remains a cornerstone of empyema care. The recent MIST2 study suggests that the combination of tPA and DNase improves pleural fluid drainage in patients with pleural infection, and is associated with a reduction in hospital stay and surgical referral. Additional studies are needed to confirm these results. Medical thoracoscopy appears to have a promising role in the early management of loculated complicated parapneumonic effusions and empyema, and further research is required. Further research is also needed to delineate the timing and indications for VATS and other surgical interventions.

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Management of Malignant Pleural Effusions

64

Andrew G. Villanueva

The development of pleural effusions is a common occurrence in patients with neoplastic disease. In one postmortem study, 15% of patients who died with malignancies were found to have malignant pleural effusions, and the annual incidence of malignant pleural effusions (MPE) in the United States is estimated to be >150,000 cases. The presence of a MPE often portends a poor prognosis; the mean survival after the diagnosis of a MPE ranges from 3 to 12 months, depending on the underlying tumor (lung cancer is generally associated with the shortest average survival time). Patients with MPE often have symptoms that impair their quality of life, such as dyspnea, orthopnea, cough, and chest discomfort, some or all of which can be improved with palliative therapeutic measures. The interventional pulmonologist can play an important role in the management of MPE by helping with the accurate diagnosis of the pleural malignancy, thereby guiding treatment plans for the underlying neoplasm, and also by performing pleural drainage procedures with or without pleurodesis to relieve symptoms.

Diagnosis

Pleural effusions may be the result of a primary neoplasm of the pleura, such as with malignant pleural mesothelioma (MPM), or from metastatic disease to the pleural surfaces. While nearly all neoplasms have been reported to cause MPE, more than 75% are caused by lung cancer, breast cancer, ovarian cancer, and lymphoma. Other types of neoplasms that can metastasize to the visceral or parietal pleura include sarcoma, melanoma, and carcinomas of the uterus, cervix, stomach, colon, pancreas, and bladder; the primary site of malignancy is unknown in about 6% of cases.

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Asbestos exposure remains the major known risk factor for MPM. While relatively few patients with a history of asbestos exposure develop the disease, up to 80% of patients with MPM have a history of asbestos exposure with a latent period between exposure and diagnosis of 20–60 years. Other possible risk factors include prior radiation exposure, infection with simian virus 40, and strong family history. The three main histological subtypes of MPM are epithelioid, biphasic, and sarcomatoid. The epithelioid subtype is the most common and carries the better prognosis, although the median overall survival ranges between 9 and 17 months.

Not all pleural effusions in patients with known malignancy are necessarily malignant pleural effusions. Patients with cancer can have "paramalignant" pleural effusions in which the effusion is not due to malignant involvement of the pleura. Potential causes of paramalignant effusions include local effects of tumor such as atelectasis due to endobronchial obstruction and postobstructive pneumonia with parapneumonic effusion, systemic effects of tumor such as venous thromboembolism and hypoalbuminemia, and complications of therapy such as radiation pleuritis and pleural effusion related to chemotherapy. It is therefore often important to make an accurate and specific diagnosis of MPE in order to make rational management decisions.

Medical Thoracoscopy/Pleuroscopy

The suspicion for MPE represents the leading diagnostic indication for medical thoracoscopy/pleuroscopy. Diagnostic pleuroscopy is often performed to evaluate an exudative pleural effusion for which no etiology can be identified despite performance of a thoracentesis with analysis of the pleural fluid and, if done, closed pleural biopsy. Pleuroscopy is particularly helpful and effective in diagnosing MPEs. In cases of suspected mesothelioma, for example, making the diagnosis can be difficult using cytological examination of pleural fluid and histological examination

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of the small samples obtained by closed-needle pleural biopsy. Pleuroscopy improves the diagnostic yield for mesothelioma to above 90%. As another example, pleuroscopy can be used in patients with known bronchogenic carcinoma who have cytologically negative pleural effusions. Since only 6% of such patients will have completely resectable tumors, medical thoracoscopy can be used to identify the small group who could potentially benefit from surgical resection while preventing surgery for the majority with unresectable disease.

The yield for diagnosing MPE by pleuroscopy ranged from 80% to 96% in reported series and a large series by Loddenkemper described a combined yield for pleural fluid cytology, closed-needle pleural biopsy, and medical thoracoscopy was 97%. The main advantage of pleuroscopy is the ability to achieve early diagnosis of MPE when pleural fluid cytology and closed-needle pleural biopsy have failed. It allows inspection of approximately 75% of the visceral pleural surface as well as of the parietal pleural surface (Fig. 64.1). Boutin reported that in 85% of patients with MPE, thoracoscopy revealed visual features suggestive of malignancy, including nodules, polypoid lesions, localized masses, thickened pleural surface, and poorly vascularized pachypleuritis. However, since appearances can be misleading – some malignancies may appear inflammatory while some inflammatory lesions can look like tumors – macroscopic diagnoses must always be confirmed by histology. Biopsies can be visually directed in instances where tumor deposits appear to be localized (Figs. 64.2 and 64.3). In addition, biopsy specimens can be obtained from multiple sites and are of greater size and depth, factors that improve the diagnostic yield (Figs. 64.4 and 64.5). The larger sample sizes increases the ability of the pathologist to make an accurate diagnosis; the pathologist, for example, can better differentiate malignant mesothelioma from adenocarcinoma and can perform special studies such as hormone receptor assays or genetic marker studies on the tissue that help determine prognosis and guide therapy.

In the past, pathologists found it difficult to make a definitive diagnosis of malignant mesothelioma without large samples obtained during open thoracotomy or autopsy. With the availability of immunohistochemistry techniques, pathologists are now better able to make the diagnosis. By permitting direct visualization of lesions, pleuroscopy facilitates the choice of biopsy sites and allows accurate assessment of the degree of involvement of the diaphragmatic, parietal, visceral, and mediastinal pleura (Fig. 64.6). Boutin reported a sensitivity of thoracoscopic biopsy of 98% for the diagnosis of malignant mesothelioma, compared with 28% for pleural fluid cytology, 24% for closed-needle pleural biopsy, and 100% for surgical biopsy.

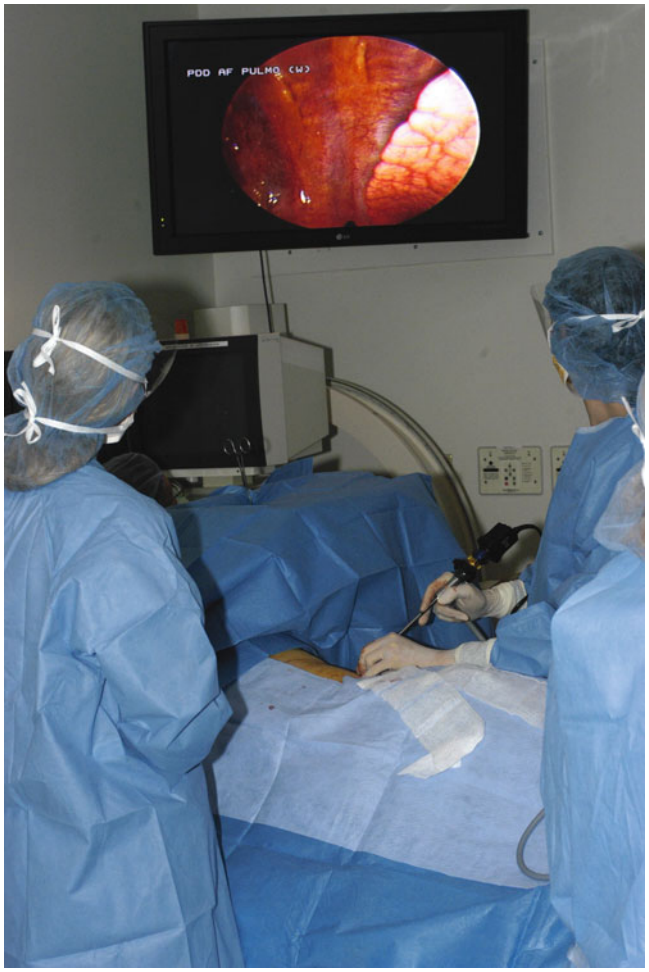

Fig. 64.1 Viewing the intrapleural space during medical thoracoscopy

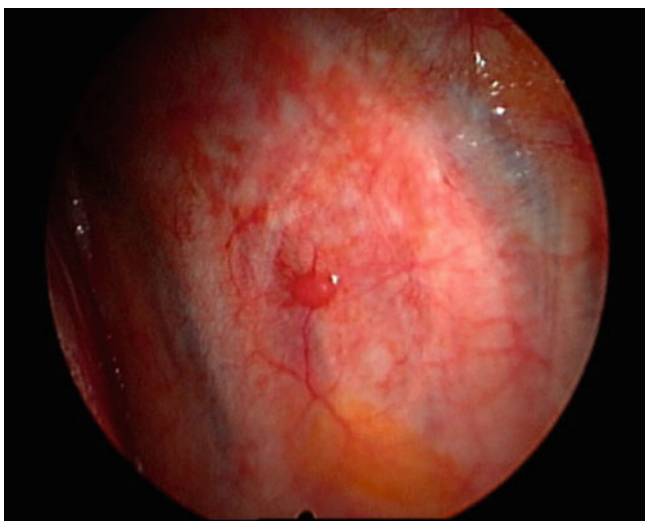

Fig. 64.2 Solitary parietal pleural tumor studding in a patient with an exudative pleural effusion of unknown etiology

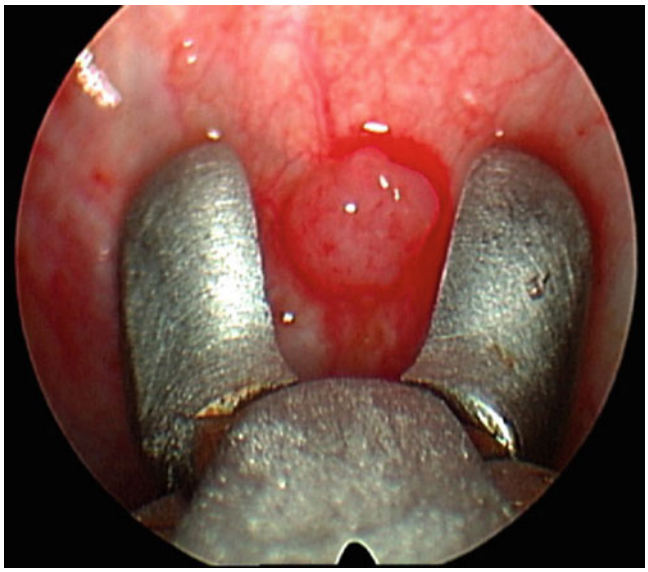

Fig. 64.3 Obtaining a biopsy of the single parietal pleural lesion under direct vision, using medical thoracoscopy. The pathology revealed adenocarcinoma from a beast primary

Bronchoscopy

The role of bronchoscopy in the diagnosis of malignant pleural effusions is limited and is not considered a routine part of the evaluation for a pleural effusion because of its low yield. A retrospective review, however, concluded that it may be useful in diagnosing bronchogenic carcinoma in patients with sizable cytology-negative pleural effusions who have hemoptysis, a lung mass, or atelectasis.

Treatment Options

While the interventional pulmonologist can play an important role in the accurate diagnosis of MPEs, an equally important, if not more frequent, role is in the treatment of MPEs. Since the presence of a MPE typically reflects advanced disease, the treatment options are generally palliative, not curative, so as to help relieve dyspnea, cough, and discomfort, thereby improving patients' quality of life.

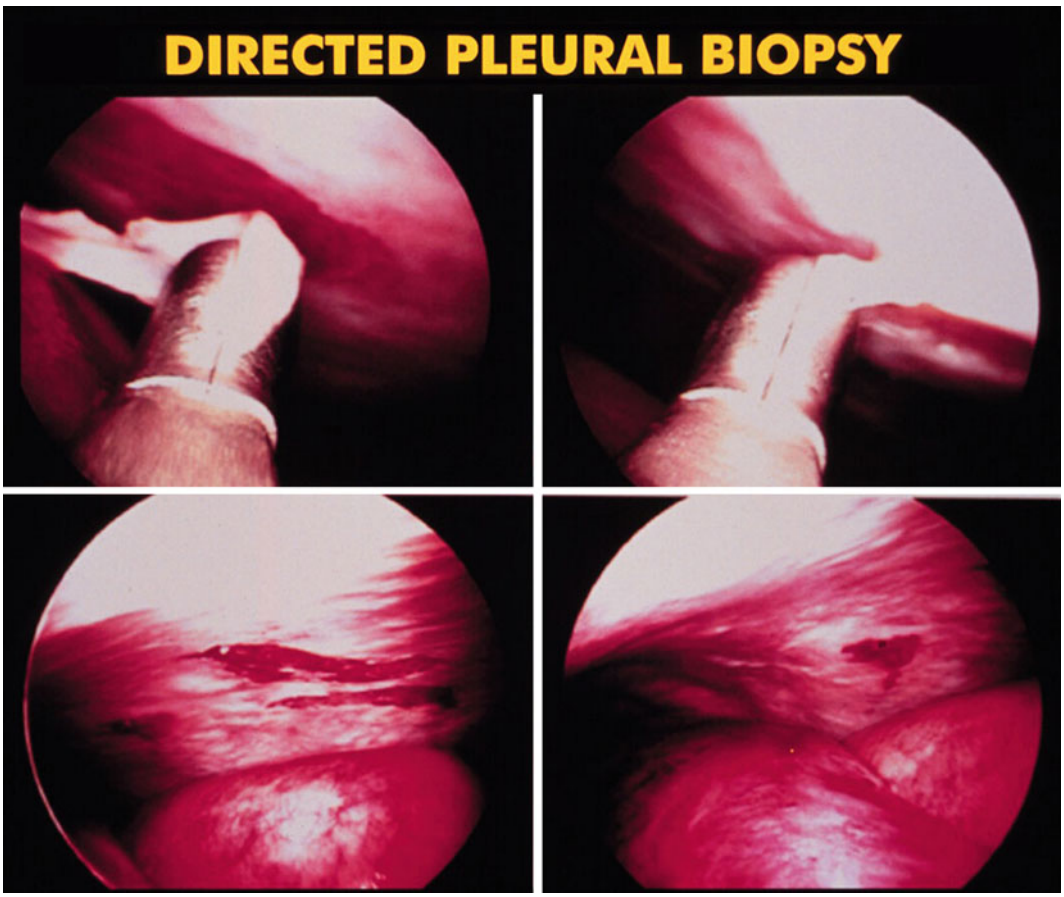

Fig. 64.4 Photo showing the sizable samples that can be obtained from the parietal pleura using medical thoracoscopy

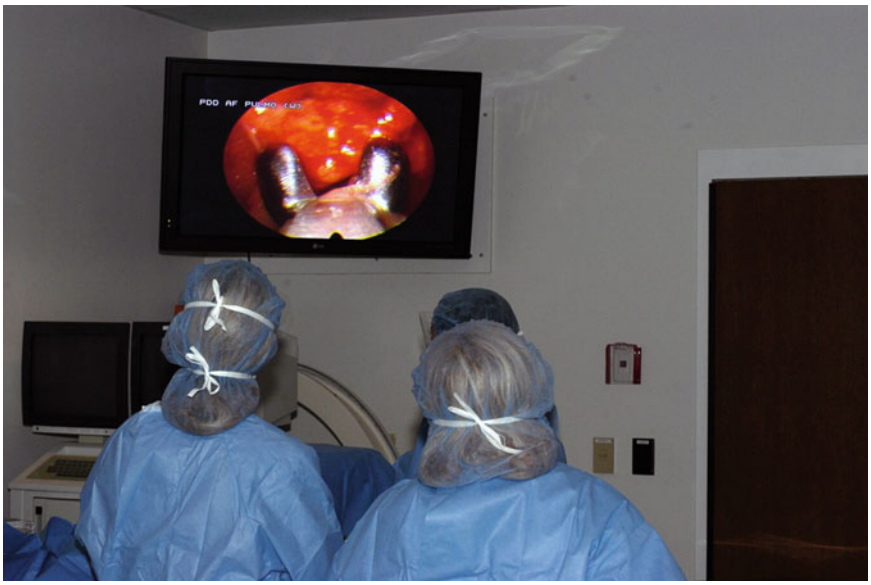

Fig. 64.5 Obtaining a parietal pleural biopsy during medical thoracoscopy

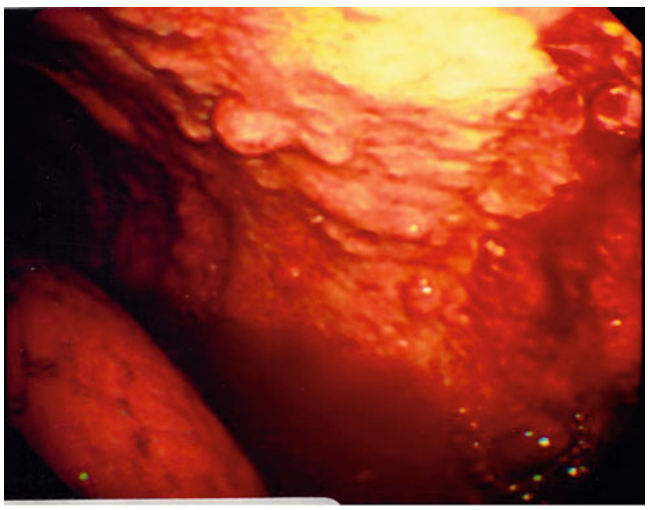

Fig. 64.6 Tumor studding along the parietal pleura. The biopsy revealed malignant mesothelioma

The cause of dyspnea, the most frequent and often the most distressing symptom, is likely multifactorial and can be due to compressive atelectasis, decreased lung compliance causing increased work of breathing, and worsened ventilation-perfusion mismatching causing hypoxemia. These problems are potentially improved by the drainage of the MPE.

Observation

Given that the treatment of a MPE is almost always palliative, directed at relieving symptoms, it is appropriate for patients without symptoms to be simply observed or treated for the underlying malignancy by an oncologist without drainage of the effusion. While many types of MPEs will not respond to chemotherapy or radiation therapy, some tumor types may respond, such as small cell bronchogenic carcinoma, lymphoma, breast adenocarcinoma, and prostate adenocarcinoma. Treatments involving drainage of the effusion, as described below, can be initiated if the MPE increases in size and begins to cause symptoms.

Therapeutic Thoracentesis

All patients with a MPE will have likely undergone a thoracentesis as part of the diagnostic evaluation. In addition to playing an integral role in the diagnosis of a MPE, thoracentesis also plays a central role in the palliative treatment when a large volume of pleural fluid is drained. Indeed, if a MPE is strongly suspected in a patient with a newly noted pleural effusion, both a diagnostic and therapeutic thoracentesis can be combined in one procedure. By draining a large volume of fluid, one can assess whether the patient's symptoms, particularly dyspnea, improve and whether the underlying lung reexpands radiographically. If symptoms significantly improve, other drainage procedures can be planned such as tube drainage and pleurodesis. If symptoms do not improve, other causes of the dyspnea should be considered, including underlying lung or heart disease, venous thromboembolism, chemotherapy- or radiation therapy-induced lung injury, tumor emboli, or pulmonary lymphangitic tumor spread. If the lung does not reexpand to touch the chest wall, one must consider pleural adhesions or lung entrapment by tumor preventing full expansion or atelectasis due to endobronchial obstruction by tumor. Such findings can affect diagnostic and treatment decisions; for example, diagnostic and therapeutic

bronchoscopy might be indicated for endobronchial tumor obstruction, or pleurodesis might not be attempted if the visceral and parietal pleural surfaces cannot be apposed because of trapped lung.

The use of ultrasound guidance for localization of the pleural effusion and to determine the optimal entry point for drainage before performing thoracentesis is becoming standard practice. Besides localizing pleural fluid, it also helps identify adhesions and fluid loculations and helps avoid puncturing visceral organs. Pleural manometry, although not yet widely adopted, can be helpful in identifying patients with trapped lung because of abnormally negative intrapleural pressures and may also help prevent reexpansion pulmonary edema by stopping drainage when intrapleural pressures exceed −20 cm H_2O (or when patients experience chest discomfort, which can be a surrogate for extremely negative intrapleural pressures.) The American Thoracic Society (ATS) and the most recent British Thoracic Society (BTS) practice guidelines continue to recommend limiting fluid withdrawal to <1.5 L during thoracentesis to avoid reexpansion pulmonary edema, in the absence of pleural manometry.

Large-volume thoracentesis is an important initial therapeutic measure for MPEs, but serial thoracentesis as the primary treatment modality is rarely a good option because of the propensity for the effusion to recur, the increased risk of multiple drainage procedures, and the increasing difficulty to completely drain the effusion because of adhesion formation and loculations with subsequent thoracenteses. In most cases, other procedures described below are generally better options because prevention of fluid reaccumulation is one of the goals of these procedures. Serial therapeutic thoracentesis should be reserved for patients with limited survival expectancy (<1 month) and poor performance status who cannot tolerate other drainage procedures.

Chest Tube Drainage and Pleurodesis

Adequate drainage of the MPE and prevention of fluid recurrence remains the main goal of the major treatment options. Prevention of fluid recurrence is most often achieved with chemical pleurodesis, which involves the instillation of a sclerosing agent into the pleural space. Several sclerosing agents have been used and described, all of which are meant to cause inflammation with fibrin deposition and consequent adhesion between the visceral and parietal pleural surfaces, thus preventing pleural fluid reaccumulation. Successful chemical pleurodesis requires the apposition of the pleural surfaces and thus reexpansion (at least partial, if not full) of the lung after pleural fluid drainage.

The two most common methods for draining the pleural fluid prior to instillation of a chemical sclerosant are chest tube drainage and thoracoscopic drainage. It had been previously assumed that large-bore chest tubes (at least a 24 F) were necessary for adequate drainage of the pleural space prior to chemical pleurodesis, but it has been shown in prospective, randomized control trials that smaller-bore chest tubes (10–14 F) provide adequate drainage with less discomfort compared to large-bore chest tubes. For chest tube drainage, the current BTS guidelines for the management of malignant pleural effusions recommend the insertion of a small-bore intercostal tube, controlled evacuation of fluid (initial drainage of 1.5 L, and 1.5 L at a time every 2 h) to prevent reexpansion pulmonary edema and radiographic confirmation of chest tube placement and lung reexpansion.

Many chemical sclerosants to achieve pleurodesis have been reported, but the most commonly used sclerosants are sterile talc, doxycycline, and bleomycin, with talc being the most commonly used. All three sclerosants can be instilled into the pleural space through a chest tube, although talc can also be instilled as a dry powder (poudrage) during medical thoracoscopy; this method will be described in the next section. The sclerosant of choice can be instilled as soon as the pleural effusion has been drained and when there is radiographic evidence of lung expansion; instillation does not need to be delayed until there is a predetermined amount of daily fluid drainage. Because the instillation of sclerosants (particularly doxycycline) is often painful to patients, lidocaine (3 mg/kg, maximum 250 mg) should be administered intrapleurally just prior to sclerosant administration, and premedication to alleviate pain and anxiety should be considered.

There have been numerous reports describing the efficacy of various sclerosing agents for pleurodesis, but there have been few high-quality comparative effectiveness trials to determine the best sclerosing agent. Meta-analyses have consistently identified talc as having the highest efficacy (whether given as a slurry through a chest tube or by poudrage during thoracoscopy) with success rates ranging from 70% to 100%. The typical dose of talc when given as a slurry is 5.0 g diluted in 50–100 ml of normal saline. Common adverse effects of talc, likely secondary to pleural inflammation, include pain and discomfort, fever (which is common and often transient), hypoxemia (in up to 30% of patients), and dyspnea. Less common side effects include pneumonia, arrhythmias, and empyema. Acute lung injury and acute respiratory distress syndrome (ARDS) due to talc has been described by several authors and does not appear to be related to dose or method of delivery but may be related to talc particle size. The talc available in Europe (mean particle size >20 μm) has not been reported to cause ARDS, as opposed to the talc available in the United States (the only FDA-approved preparation is Sclerosol®), which contains particles <10 μm. It has been hypothesized that talc with smaller particle sizes (<10 μm) can be systemically absorbed into the vascular beds and cause an inflammatory reaction in the lung resulting in an acute pneumonitis or ARDS. The incidence of respiratory failure in patients with MPE receiving talc slurry for pleurodesis

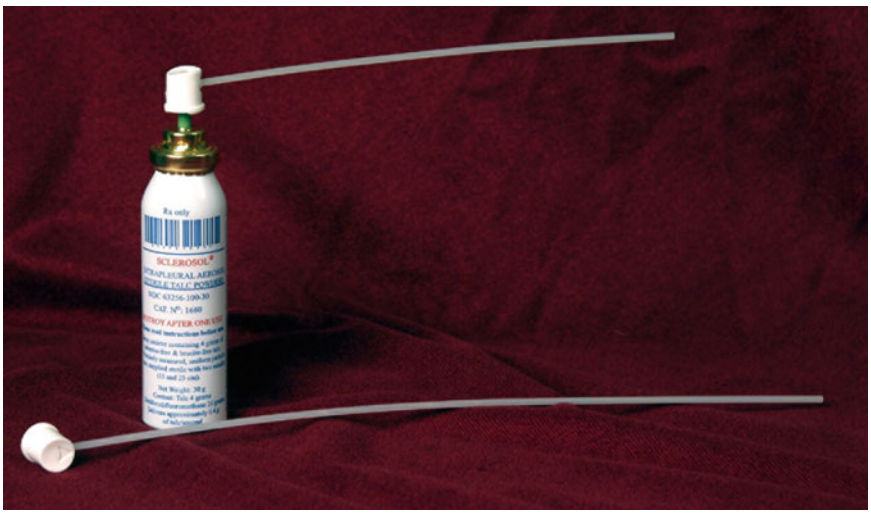

Fig. 64.7 Sterile talc that has been sterilized and packaged in a pressurized canister (Sclerosol®) for talc poudrage during medical thoracoscopy

was 4% in a prospective randomized trial. Despite the potential adverse effects, talc remains the most commonly used pleural sclerosant because of its wide availability, low expense, and good efficacy.

Tetracycline had been frequently used as a chemical sclerosant until its production ceased in the early 1990s. Doxycycline has been used as a substitute for tetracycline with successful pleurodesis rates of 60–81%. Common side effects include fever and pain, which can be severe and makes the use of intrapleural lidocaine and analgesics all the more important when using doxycycline. A typical doxycycline dose is 500 mg diluted in 50–100 ml of sterile normal saline instilled through the chest tube.

Bleomycin is an effective sclerosant with successful pleurodesis rates reported at 58–85%. Common side effects include fever, chest pain, and cough. It is not used commonly in the United States because of its relatively high cost, especially compared to talc, and its lack of demonstrated superiority over talc.

It is common practice to rotate the patient to different positions after instillation of the sclerosant to ensure intrapleural dispersion, but prospective studies have shown no advantage of rotational maneuvers over simply clamping the tube for 2 h. It has also been customary to remove the chest tube when daily pleural fluid drainage has fallen below a threshold level, such as 100–150 ml per day, but it is possible to remove it sooner as long as the chest x-ray shows adequate drainage for the effusion without diminishing effectiveness.

Thoracoscopic Drainage and Pleurodesis

Medical thoracoscopy can be used to achieve pleurodesis by completely draining the pleural space and instilling the sclerosing agent under direct vision, usually dry talc delivered as a poudrage (see Figs. 64.7 and 64.8). There are several theoretical advantages to thoracoscopic talc insufflation compared with talc slurry sclerosis. Medical thoracoscopy allows complete effusion drainage under direct visualization and optimal chest tube positioning. Talc is insufflated in a manner that allows even distribution over the entire visceral and parietal pleural surfaces. In contrast, the slurry of water-insoluble talc may gravitate to the dependent part of the pleural space shortly after instillation. Finally, in patients with an underlying malignancy but negative fluid cytology, parietal pleural biopsies of suspicious areas can be taken at the time of medical thoracoscopy, before proceeding with pleurodesis. A systematic review comparing the various treatment options to achieve pleurodesis in patients with MPE was published in the *Cochrane Database* in 2004. The comparison of thoracoscopic talc pleurodesis (TTP) and talc slurry pleurodesis favored thoracoscopic pleurodesis, with a relative risk for nonrecurrence of the effusion of 1.19 (95% CI, 1.04–1.36).

A large, multicenter randomized trial comparing talc poudrage with talc slurry was conducted by the North American Cooperative Oncology Groups in which a total of 482 patients were randomized to thoracoscopy with talc insufflation (n = 242) or tube thoracostomy with talc slurry (n = 240). Overall, no difference was detected in the percentage of patients with successful pleurodesis at 30 days (78% for TTP and 71% for talc slurry). However, in the subgroup of patients with primary lung or breast cancer, the success rate of TTP was found to be significantly higher than with talc slurry (65% vs. 50%, p = 0.014). Lung cancer and breast cancer are the first and second most common neoplasms causing malignant effusions, and these findings suggest that TTP may be a better option for a large proportion of patients

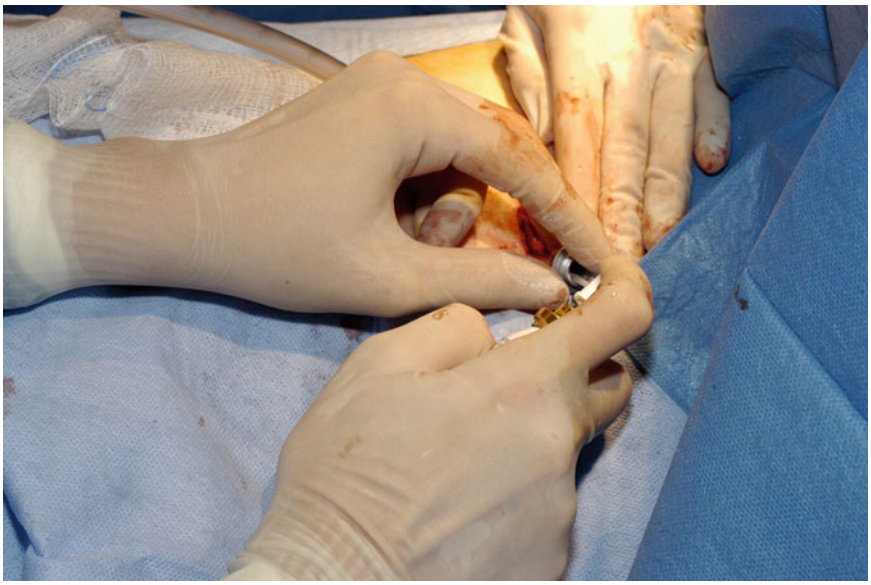

Fig. 64.8 Performing talc poudrage using Sclerosol® during medical thoracoscopy

with MPE. Moreover, a subgroup analysis of those patients with lung cancer or breast cancer who achieved lung expansion after drainage of the fluid (and therefore did not have radiographic evidence for trapped lung) and were alive at 30 days showed that TTP achieved successful pleurodesis more frequently compared to talc slurry (82% vs. 67%, $p=0.022$).

The most common side effects reported with TTP are pain and fever. In a detailed review of pleurodesis agents, pain following talc insufflation occurred in 7% of patients and fever occurred in 16% of patients. The fever has been shown to be related to the talc and not to the thoracoscopy. Empyema following TTP has been reported in 0–3% of patients, and local site infection is uncommon. Cardiovascular complications reported with TTP include arrhythmias, cardiac arrest, chest pain, myocardial infarction, and hypotension; these may be attributable to the procedure and not talc per se. Death directly related to medical thoracoscopy is extremely rare.

As described earlier, talc has been associated with acute lung injury and, rarely, ARDS and respiratory failure. In a recent single-center retrospective review of 138 patients undergoing TTP using Sclerosol®, the incidence of talc-related acute lung injury was at least 2.8% and possibly 5.6%.

Safe and successful TTP depends, in large part, on judicious patient selection. It should be demonstrated that drainage of the fluid results in symptom relief, that pleurodesis is achievable since the lung is expandable, that the patient can tolerate moderate sedation required for thoracoscopy, and that the patient can tolerate the procedure itself. In a study examining predictors of survival in patients with symptomatic MPE referred for TTP, the authors concluded that performance status, as measured by the Karnofsky score, was the best predictor. The authors proposed that a Karnofsky score ≥70 (which reflects a patient who is ambulatory and living independently) may be a reasonable marker for deciding which patients with MPE should undergo TTP. In patients with MPE, overall prognosis should thus be considered in the selection of patients for TTP. As an example, a patient with MPE who has a Karnofsky score of ≥70 and an expected prognosis of more than 6 months might be an excellent candidate for TTP, whereas other options (such as tunneled pleural catheters, which will be described later, or palliative care) should be considered for a patient with a poor performance status and an expected survival of less than 1–2 months.

It has been standard practice to hospitalize patients after pleuroscopy and talc poudrage with a chest tube in place until pleural drainage has diminished to <100–150 ml/day; this typically requires hospitalization for 6–7 days. A recent pilot study in which a tunneled pleural catheter (described in more detail below) was placed at the time of medical thoracoscopy and left in at the time of patient discharge for frequent, intermittent drainage showed that pleurodesis was achieved in 92% of 30 patients. The median duration of hospitalization following the procedure was 1.79 days, and the tunneled pleural catheter was removed at a median of 7.54 days. The placement of a tunneled pleural catheter at the time of medical thoracoscopy and talc poudrage can potentially allow earlier discharge and shortening of a hospitalization.

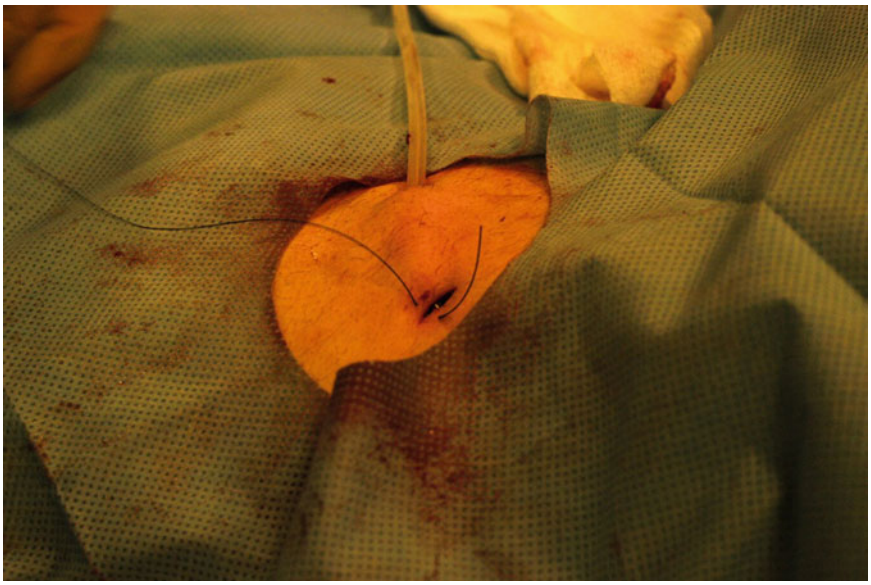

Fig. 64.9 Completing the placement of an indwelling tunneled pleural catheter

Indwelling Tunneled Pleural Catheter

Another option for the treatment of patients with symptomatic MPEs includes the placement of an indwelling tunneled pleural catheter (TPC), which can be placed at the bedside, using only local anesthesia (Fig. 64.9). A major advantage of using a TPC is that it can be placed in the ambulatory setting, making hospitalization unnecessary and allowing the patient to return home. Furthermore, it has been reported that pleurodesis can occur even without the instillation of sclerosant. It may also be useful in relieving dyspnea in patients with trapped lung in whom pleurodesis cannot be achieved. It does require knowledge of basic sterile technique and the intermittent drainage of pleural fluid through the TPC by the patient or the patient's caregiver.

There had been a previous report showing the feasibility and efficacy of using a small-bore pigtail catheter for drainage and pleurodesis in the outpatient setting. The introduction of a commercially available TPC and accessories led to its widespread adoption and case series reports of its clinical effectiveness. Symptom relief is frequently achieved, even in the presence of trapped lung, and spontaneous pleurodesis occurred in 42–58% of patients. The major risk of the TPC was infection with cellulitis (1.6%) and empyema (3.2%). Other potential complications include loculation of fluid and catheter blockage, pneumothorax, tumor seeding, and bleeding.

There are few studies comparing the effectiveness of using TPC to other methods of drainage and pleurodesis. One descriptive study showed the use of TPC to be an effective alternative method in patients with trapped lung in whom thoracoscopic talc pleurodesis was not a good option. A randomized study compared the use of TPC to doxycycline pleurodesis using a standard intercostal tube in the management of MPE and found shorter hospitalizations, a spontaneous pleurodesis rate of 46% at a median of 26.5 days, and a similar late recurrence rate (13% vs. 21%).

The use of TPC should be considered in symptomatic patients with MPE when there is trapped lung and evidence of symptom relief with fluid drainage, the patient has a poor performance status and therefore a poor candidate for medical thoracoscopy, or in patients who prefer to avoid hospitalization for chest tube drainage and pleurodesis.

Palliative/Hospice Care

All of the aforementioned therapeutic options for MPE are considered palliative since the goal is relief of dyspnea. For patients with poor performance status and extremely poor prognosis, it may be reasonable to forgo any drainage procedure and focus solely on comfort measures, using opiate analgesics and anxiolytics as required. Hospice care, either as an inpatient or outpatient, may be the most appropriate option in some circumstances.

Treatment Algorithm

See Fig. 64.10.

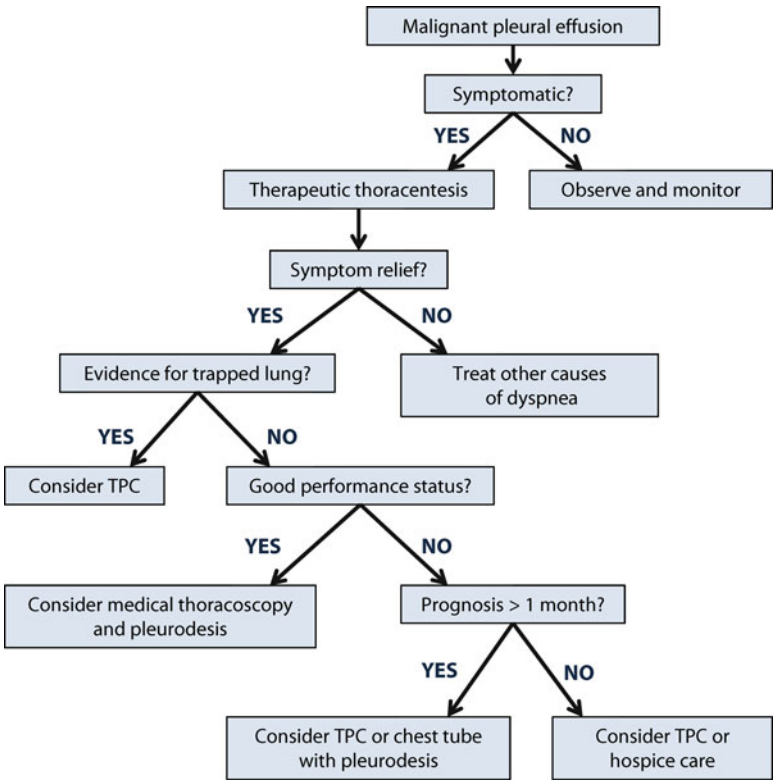

Fig. 64.10 Suggested algorithm for the treatment of patients with malignant pleural effusions (TPC = tunneled pleural catheter)

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Approach to Unclear Exudates

65

Gaëtane Michaud

Definition of an Unclear Exudate

A pleural effusion is considered an unclear exudate if the pleural fluid collection meets Light's Criteria for an exudative effusion and no cause is identified despite an attempt to identify the cause. A search for the etiology of the effusion includes a comprehensive history and physical examination, serologies, imaging, and pleural fluid analysis. To differentiate between an unclear exudate and an idiopathic pleural !effusion, the latter meets all of the criteria of an unclear exudate, and in addition, pleural biopsy fails to elucidate the cause of the effusion.

Epidemiology of Pleural Effusions

The exact prevalence and incidence of pleural effusions is unknown and is dependent on the population studied. It is estimated that the annual incidence of pleural effusions exceeds 1.5 million in the United States alone. Of those, congestive heart failure accounts for 500,000, parapneumonic 300,000, and cancer 200,000. Other less common causes include pulmonary embolus 150,000, viral 100,000, post-cardiopulmonary bypass 60,000, and hepatic hydrothorax 50,000. Of note, these figures are approximations and do not account for patients that did not benefit from thoracentesis. Worldwide, parapneumonic effusion is likely to be the most prevalent; however, in some specific populations, (i.e. those with a known underlying malignancy), it is most probable that the effusion is attributable to the cancer.

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Pathophysiology of Pleural Fluid Accumulation

Pleural fluid is produced at a rate of approximately 15 ml/day. There exists a constant turn over with fluid being secreted from the pleura and then reabsorbed via the lymphatics. Due to the dynamic process and high capacity for fluid reabsorption, the basal fluid production rate must exceed 30 times its normal rate prior to fluid accumulation. As a result of this high capacity for fluid resorption, the majority of effusions are thought to result from a combination of increased fluid production and reduced transit from the pleural space.

Broadly, effusions are broken down into exudates and transudates based on the mechanism of fluid accumulation. Exudates are the results of capillary leak of proteins into the pleural space, whereas transudative effusions are low-protein fluid collections. Often transudates are the result of increased microvascular hydrostatic pressure as opposed to the reduction in oncotic pressure seen in exudative effusions.

Differentiation of Exudates from Transudates

As stated above, pleural effusions are clinically divided into exudates and transudates based on the composition of the pleural fluid. Light developed a set of criteria stratifying the effusion by protein and lactate dehydrogenase (LDH) levels. In general, an effusion is considered an exudate if it meets at least one of Light's Criteria. There are a total of three criteria comparing pleural fluid to serum ratios of both total protein and LDH as well a concentration of LDH compared to the serum upper limit of normal. Refer to Table 65.1 for Light's Criteria. A meta-analysis performed by Heffner et al. evaluated the accuracy of Light's Criteria as well as other potential tests to discriminate exudates from transudates in 1,448 patients with pleural effusions and found a diagnostic accuracy ranging between 86% and 95% (Table 65.2). No test fared better than Light's Criteria, and therefore, it remains the gold standard for pleural fluid classification with a combined sensitivity of 98.8%, specificity of 77.8%, and

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Table 65.1 Light's criteria

Light's criteria	Value
Pleural fluid to serum protein ratio	>0.5
Pleural fluid to serum LDH ratio	>0.6
Pleural fluid LDH concentration	>2/3 upper limit of lab normal value

Table 65.2 Studies evaluating light's criteria

Study	Sensitivity	Specificity	Accuracy	PPV	NPV
Light (1972)	99	98		99	98
Meisel (1990)	90	82	86	87	
Roth (1990)	100	72			
Valdez (1991)	95	78	91	95	80
Romero (1993)	98	77	95		
Burgess (1995)	98	8,378	93	93	96
Costa (1995)	98	82			
Vives (1996)	99	78	95	95	93

diagnostic accuracy of 94.7%. A small subset of patients has what is often referred to as a pseudoexudate. These are most often patients with congestive heart failure having been treated with diuretic therapy sometimes resulting in significant changes in the pleural fluid's chemistry. The result is an effusion that may have initially been classified as a transudate, but following diuresis meets criteria for an exudate. In these cases, the albumin gradient (serum albumin minus pleural fluid albumin >1.2 g/dl) may be helpful to determine whether the fluid is consistent with a transudate. Another consideration would be a pro-BNP (natriuretic peptide) level to determine if the underlying diagnosis is heart failure.

Causes of Pleural Effusions

The differential diagnosis of pleural effusions is extensive which at least partially explains the need to divide effusions into exudates and transudates to reduce the diagnostic possibilities.

The most common causes of transudative effusions include congestive heart failure and cirrhosis. Other less common causes include renal disease (nephrotic syndrome, glomerulonephritis, and peritoneal dialysis), hypoalbuminemia, and myxedema. In less than 10% of cases, malignant effusions may be transudative as are less than 35% of effusions related to pulmonary emboli. With respect to exudative effusions, the most common causes include malignancy (either primary lung or metastatic), infectious (parapneumonic, empyema, or pleural tuberculosis), connective tissue diseases, and post-cardiopulmonary bypass. Refer to Table 65.3 for a comprehensive list of causes of transudative and exudate effusions.

Table 65.3 Causes of transudative versus exudate pleural effusions

Transudative	Exudative
– Congestive heart failure	– Malignancy
– Nephrotic syndrome	Primary, mesothelioma, or metastatic
– Cirrhosis	– Infection
– Hypoalbuminemia	Parapneumonic, empyema, or tuberculous
– Peritoneal dialysis	– Connective tissue disease
– Glomerulonephritis	Systemic lupus, rheumatoid arthritis
– Urinothorax	– Post-coronary artery bypass graft
– Atelectasis	– Pulmonary embolism
– Trapped lung	– Chylous
– SVC obstruction	Disruption of thoracic duct or lymphoma
– Constr. pericarditis	– Subdiaphragmatic
– Malignancy (<5%)	Pancreatitis, abscess, or benign ovarian tumor
– Pulmonary embolus (<35%)	– Yellow nail syndrome
– Myxedema	– Medication related
– Sarcoidosis	– Benign asbestos pleural effusion

Clinical Approach to Pleural Effusion

A comprehensive history and physical examination are essential in the evaluation of patients with pleural effusions. In many cases, the cause of the effusion may be suspected based simply on the findings of the clinical assessment obviating the need for further diagnostic testing. If, for example, a patient has evidence of congestive heart failure, then it is quite appropriate to treat the heart failure as a therapeutic challenge to determine whether the effusion is responsive to diuretics. In the case of a refractory effusion in this setting, then one may consider a more extensive diagnostic work-up of the effusion.

Pleural effusions often present with dyspnea depending on the size of the effusion at presentation. Pleuritic chest pain however may be indicative of pleural inflammation from causes such as infection, pulmonary emboli, or serositis. When pleurisy is associated with other symptoms of infection such as productive cough and fever, then one must be suspicious of a parapneumonic effusion or empyema. The presence of constitutional symptoms may suggest a systemic disease, chronic infections such as tuberculosis or alternatively malignancy. In addition, hemoptysis may be concerning for malignancy or pulmonary emboli. An extensive exposure and travel history may suggest malignancy, asbestos-related pleural disease, or tuberculosis. Past medical and family history may also be quite revealing as well as a careful overview of the patient's medication list. The list of medications leading to pleural effusions is quite lengthy and

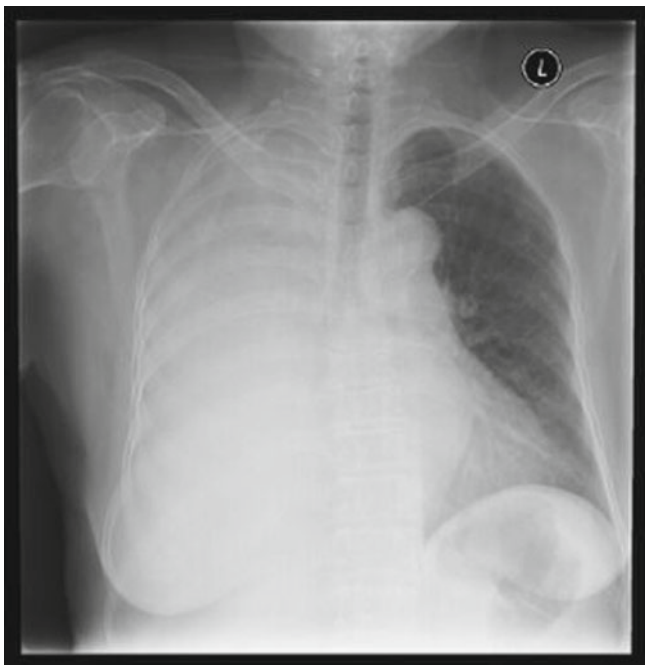

Fig. 65.1 Posteroanterior chest projection of a patient with a large pleural effusion and an obstructing endobronchial lesion resulting in the mediastinum being fixed in the center as well as a cutoff sign of the right main bronchus

beyond the scope of this review. The website www.pneumotox.com is a valuable resource to identify pulmonary and pleural manifestations attributable to medications.

Systemic manifestations should be sought out as they may lead to a diagnosis of connective tissue disease, hypothyroidism, or heart failure. Concern should be raised for inflammatory, infectious causes, or pulmonary infarct if the patient presents with a pleural friction rub. Another consideration is the size and symmetry of the pleural effusion. Nearly 70% of massive effusions are malignant. Bilateral effusions are most suggestive of congestive heart failure although may be present in malignancy, connective tissue disease, drug reactions, infection, and renal disease.

Chest Imaging

Chest imaging can provide invaluable information regarding the nature of the pleural effusion. This includes the location, size, and flow characteristics of the effusion. The posteroanterior (PA) film is the standard first-line imaging technique and is able to identify even a small quantity (approximately 200 ml on PA and 50 ml on lateral projection) as blunting of the costophrenic angle. As stated above, very large fluid collections are most commonly attributable to malignancy. The plain radiograph may also give clues as to the etiology of the effusion, for example, an obstructing lesion in the bronchus (Fig. 65.1).

The role of computed tomography (CT) in the management of patients with unclear exudates is limited to the identification of other pathologies that may be leading to the pleural effusion. The decision to perform a CT of the chest will depend on the clinical context and suspicion of an etiology requiring this procedure for diagnosis, for example, pulmonary embolus. Additional imaging may also be beneficial should the pleural fluid analysis fail to reveal the cause of the effusion.

Pleural Fluid Analysis

Fluid Characteristics

Pleural fluid analysis is the first initial invasive diagnostic test to be performed in an undiagnosed pleural effusion. The approach to thoracentesis is the subject of different section of this text and therefore will not be discussed in detail.

Gross inspection of the pleural fluid can be predictive of the cause of the accumulation. The usual appearance of pleural fluid in health is clear and straw colored. This may also be the case in exudative effusions. If the fluid is milky looking, then one may consider a chylothorax, which can be seen with yellow nail syndrome. Turbid fluid particularly if foul smelling (anaerobes) may suggest a complicated parapneumonic effusion or empyema. Serosanguinous or frankly bloody effusions may be seen with malignant pleural effusions, effusion following coronary artery bypass, benign asbestos pleural effusion, pulmonary emboli (particularly if pulmonary infarct), and traumatic chest injury. In order to distinguish between a frank hemothorax and simply a bloody effusion, a specimen may be sent for hematocrit. If the pleural fluid to serum hematocrit ratio exceeds 0.5, then it meets criteria for a hemothorax, and the patient may require further evaluation to determine if there is ongoing blood loss. Normally, the pleural fluid is relatively odorless; however, as mentioned above, a foul odor may suggest an anaerobic or polymicrobial infection of the pleural space. Also, in the case of urinothorax, the fluid may smell of ammonia.

Cell Count and Differential

A cell count and differential should be performed in all cases of exudative effusions of unknown etiology. The diagnostic possibilities considering an elevated red blood cell count (>100,00 per mm^3) on pleural fluid analysis were discussed above. With respect to a high white blood cell count (>10,000 per mm^3), the vast majority of these cases represent empyema. On the differential, eosinophilia (>10%) may suggest a drug reaction, air or blood contaminating the pleural space. Lymphocyte predominant effusions (>50%) may be worrisome for malignancy, connective tissue disease, tuberculosis,

pulmonary emboli, and post-cardiopulmonary bypass-related effusions. Very high lymphocyte counts (>90%) are seen most commonly with malignancy, tuberculosis, or rheumatoid pleurisy. Pleural fluid neutrophilia (>50%) is often attributable to pleural space infections and subdiaphragmatic pathologies.

Other Routine Tests

LDH and protein pleural and serum levels should be sent to ensure that the effusion does indeed meet Light's Criteria for an exudative effusion as discussed above (Table 65.1). A low pleural fluid glucose (<60 mg/dl) may be seen in the context of a parapneumonic effusion or empyema, tuberculous effusion, malignancy, or rheumatoid pleurisy. A pH of less than 7.2 is again concerning for parapneumonic effusion or empyema, malignancy, and tuberculosis in addition to esophageal rupture. Cytology is essential although the yield ranges between 40% and 80% with multiple samples. Gram stain and culture should be performed and may lead to the identification of a microbe in the context of a pleural space infection. Of note, pleural fluid analysis by Ziel-Nielsen stain for tuberculosis is quite poor, and therefore in the context of a high index of suspicion, the recommendation is to consider either adenosine deaminase testing or pleural biopsy.

Special Tests

Some additional tests may be considered in the appropriate clinical context. If there is concern that the effusion may be a chylothorax based on its gross appearance, a triglyceride level should be measured on the pleural fluid. A level greater than 110 mg/dl is diagnostic, and possibility of traumatic disruption of the thoracic duct, lymphoma, or yellow nail syndrome should be explored. Amylase is another useful test under the right circumstances. Subdiaphragmatic processes such as pancreatitis, salivary gland tumors, and esophageal rupture can lead to an elevated (above upper limit of serum normal serum value) amylase level in the pleural fluid. If tuberculosis is a consideration, the special tests that may be considered include adenosine deaminase (ADA), interferon gamma (INF), and polymerase chain reaction (PCR). ADA (>40U/L) in a lymphocyte predominant effusion is highly suggestive (>90%) of a tuberculous effusion and is routinely used in high prevalence countries as the mainstay of diagnosis for TB pleurisy. The role of pleural INF levels is mainly in the context of a high level of suspicion but ADA either unavailable or results not confirmatory. PCR can be helpful for pleural space infections although its role is limited by high false-positive rates. In advent of targeted cancer therapies, pleural fluid may be sent for cell block and then tumor markers identified, for example, estrogen/progestin receptor status, HER-2/neu, or CA-125.

Considering the low yield on a single pleural fluid analysis, it is recommended to repeat the thoracentesis and pleural fluid analysis at least once prior to moving to more invasive testing. No further incremental benefit is derived from sending pleural fluid cytology more than three times. Despite standard pleural fluid analysis, 25% of exudative effusions remain undiagnosed.

Optional Minimally Invasive Tests

If there is consideration of an endobronchial lesion, a flexible bronchoscopy should be performed. A CT-angiogram may be performed if there is a suspicion of pulmonary embolus. Finally, an electrocardiogram and echocardiogram may be revealing if a cardiac etiology of the exudative effusion is being considered.

Pleural Biopsy

Several options exist for pleural biopsy. These include conventional closed pleural biopsy, a transthoracic needle biopsy, or a biopsy under direct visualization via thoracoscopy. The yield of the various techniques is dependent on the extent and distribution of the pleural involvement. Unless the pleura are very diseased, pleural involvement is often patchy. In addition, the disease may involve visceral pleura, parietal pleura, or both.

Closed Pleural Biopsy

Closed pleural biopsy is a procedure performed under local anesthesia similar to thoracentesis. A small incision is made into the skin to facilitate the passing of a needle that is advanced through the chest wall using a corkscrew motion until breeching the parietal pleura. The cutting edge of the needle is anchored on the rib below and using a guillotine action is used to excise a piece of the parietal pleura. Several needles exist for this purpose; however, the most widely used include the Abrams and Cope needles. The yield of closed pleural biopsy varies depending on the etiology. Its greatest yield is for TB and is in the range of 70–80% in high prevalence populations. Unfortunately, the yield for malignancy as well as other pathologies is much lower, less than 45%. When this procedure is combined with other diagnostic modalities such as pleural fluid analysis or thoracoscopy, it adds little to the diagnostic accuracy outside of tuberculosis. The frequency of use of this procedure in the US is quite limited. To establish and maintain competence requires the

operator to perform five proctored procedures and then an additional five per year to maintain competency. Despite this low number of procedures, a minority of physicians receives adequate training or performs sufficient numbers of procedures to establish or maintain competence.

Transthoracic Needle Biopsy

Transthoracic needle biopsies are usually performed under CT guidance using either a Tru-cut biopsy or Abrams needle. The sensitivity of CT-guided pleural biopsy in malignancy was shown to be 87% using a cutting needle, compared to 47% by closed pleural biopsy. The CT guidance allows the biopsy to be directed to sites of pleural abnormalities; however, subtle pleural changes may not be evident with this form of imaging.

Thoracoscopy

Due to the relatively high number of undiagnosed exudative effusions even after extensive pleural fluid analysis and the low additional yield of closed pleural biopsy, patients often require thoracoscopy. Medical thoracoscopy or pleuroscopy is a minimally invasive procedure by which an optic is passed through a port into the pleural space. This allows for a thorough inspection of both visceral and parietal pleura as well as a biopsy of abnormalities under direct visualization. Medical thoracoscopy is the topic of a complete chapter in this text; therefore, discussion will be limited to the use of this modality in the management of unclear exudates.

As stated above, the major advantage of medical thoracoscopy for the diagnosis of undiagnosed exudates is that it allows the operator to identify clearly abnormal areas of the pleura to biopsy for diagnosis. We previously mentioned that pleural disease tends not to be uniform, therefore explaining the increased yield of this procedure as compared to pleural fluid analysis or closed pleural biopsy. As is the case for most procedures, the diagnostic yield of direct pleural biopsy via thoracoscopy is dependent on the cause of the effusion. Large retrospective cohort studies of several thousand patients have shown that for malignancy, the sensitivity is in the range of 93–95%, whereas for tuberculosis, it approaches 100%. Biopsy of the pleura for tuberculosis often will reveal noncaseating granulomas and acid-fast bacilli are identified on tissue culture. Again, histopathology offers the major advantage of large tissue samples for additional testing necessary to evaluate for mutations or eligibility for immune therapies.

Natural History of Unclear Exudates

A small subset of patients, approximately 15–20%, will be given a pathologic diagnosis of nonspecific pleuritis following thoracoscopy. A natural history study of patients with this diagnosis was performed at total of 68 patients were followed for a mean time of 33 months (range 3–110 months). Forty-eight patients had a suspected diagnosis, while the remaining 20 had no probable diagnosis. Of these 68 patients, 6 were lost to follow-up (two with a probable cause and four without a probable cause) and two without a probable cause died during the period of study. Neither of the deaths was attributable to either the thoracoscopy or the pleural effusion. Only five patients (8%) were found to have cancer (two primary lung and three mesothelioma), while the other 92% followed a benign course.

In another study of 142 patients with undiagnosed exudative effusion despite comprehensive work-up, all patients underwent medical thoracoscopy. Of these, the diagnosis of nonspecific pleuritis was made in 31% (n=44). Only five patients (11%) of the patients with nonspecific pleuritis were eventually diagnosed with malignancy. The patients were followed until death or a mean of 21 months, and the other 39 patients in the subgroup of nonspecific pleuritis all followed a benign course.

A Spanish group performed a 10-year prospective cohort study of patients with idiopathic pleural effusion. This included a total of 40 patients followed for a mean of 62 months (range 26–108 months). Eighty percent of cases elucidated no diagnosis despite the protracted follow-up period. Of the remaining eight patients, the following diagnoses were eventually made: benign asbestos pleural effusion in three and one each of non-small cell lung cancer, mesothelioma, heart failure, cirrhosis, and rheumatoid arthritis. Spontaneous resolution of the effusion occurred within 5.8 months in all patients (median 1.7 months). Five patients had one or more relapses over the period of study. Further diagnostic work-up including pleural fluid analysis was performed at each relapse and failed to identify the cause. The majority of patients followed a benign course, and the authors concluded that a conservative approach to undiagnosed exudative effusions is warranted.

Summary

In summary, the literature discussing the optimal approach to unclear exudates is limited; however, nearly all suggest that only a minority remain undiagnosed after following a comprehensive work-up (Fig. 65.2) including a detailed history

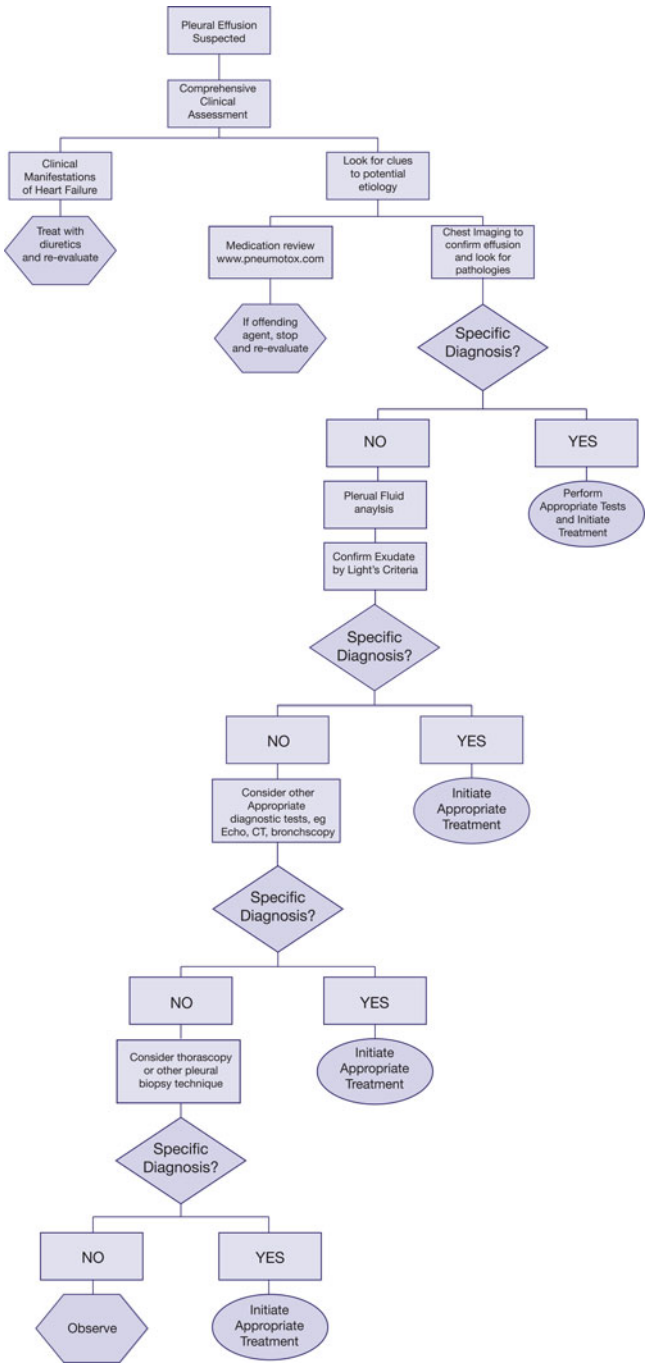

Fig. 65.2 Algorithm for the systematic evaluation of unclear exudative effusions

and physical examination, careful review of medications and exposures, and appropriate diagnostic testing, only a minority remain undiagnosed. Protracted follow-up of these patients after thoracoscopy reveals a relatively indolent course for the majority with only occasional relapses. The concern regarding a missed diagnosis with significant negative consequences such as an occult malignancy hardly seems justified. In fact, the data would suggest that a conservative approach of watchful waiting is quite appropriate.

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Part V

Airway Access Techniques

Percutaneous Tracheotomy

66

Lonny Yarmus

History of Tracheotomy

Tracheotomy is one of the oldest documented surgical procedures performed. Two slabs over 3,500 years old dated to be from the beginning of the first Egyptian dynasty depict early tracheotomy. A seated person with a lancet to be used to puncture the tracheotomy is pointed at the neck of an individual with the person's hands tied behind their back. The slabs, depicted below (Figs. 66.1 and 66.2), also show the symbol Ankh, which represents life, and the Lancet which in ancient Egypt was used as a symbol representing the ability to breathe.

The procedure was also performed in the ancient Hindu culture and described in the Rig Veda, the sacred Hindu book of medicine written between 2000 and 1000 B.C. Alexander III of Macedon more commonly known as Alexander the Great (356–323 B.C.) reportedly performed a tracheotomy on one of his soldiers and "opened the trachea of a choking soldier with the point of his sword." The prominent Roman surgeon Galen of Pergamon (130–200 B.C.) wrote that his colleague Asclepiasds of Bithynia performed the first elective tracheotomy. Early evidence of the procedure surfaced again in the medical text *Epitome* written by Paul of Aeginas (625–690 B.C.) with this description of tracheotomy: "In cases of inflammation of the mouth or palate, it is reasonable to use tracheotomy (pharyngotomy) in order to prevent suffocation. We cut the trachea below the upper part at the level of the third or fourth ring. For a better exposure of the trachea, the head needs to be reclined. A transverse incision is made in between two tracheal rings, so it is not the cartilage that is incised, but the tissue in between." The procedure was deemed a success by "a wheezing noise escaping from the hole in the trachea and the loss of the patient's voice." For unknown reasons, the procedure fell out of favor during the fifth century, and its use was rarely documented over the next millennium. tracheotomy reemerged in the medical literature in 1546 when the Italian surgeon Antonia Musa Brasavola is credited with reintroducing the procedure on a patient dying from asphyxiation from an upper airway obstruction and is quoted as saying, "when there is no other possibility, in angina, of admitting air to the heart, we must incise the larynx below the abscess." Hieronymus Fabricus (1537–1619) is credited with first using a cannula which was short and straight so as to reduce the risk of posterior tracheal wall puncture and flanges to prevent aspiration of the instrument.

In 1626, another Italian surgeon, Sanctorio Sanctorius, performed the first percutaneous approach to tracheotomy and described the procedure by using a "ripping needle" to introduce a silver cannula into the tracheal lumen and then removed the needle. Despite the technical improvements in regard to the procedural approach to tracheotomy, it remained a highly morbid procedure leading to the majority of practicing surgeons to shy away from performing it. This most famously occurred on the evening of December 14, 1799, when a patient was fatally struck with "cynanche trachealis" presumed to be bacterial epiglottitis. He was surrounded at the bedside by 3 prominent physicians, Dr. James Craik, Dr. Gustav Brown, and Dr. Elisha Dick. At the time, bloodletting was a mainstay treatment and tracheotomy was still considered experimental. Dr. Dick had recently been trained in tracheotomy and reportedly a debate ensued between Dr. Dick and Dr. Craik in regard to the appropriate treatment. As the senior physician on the team, Dr. Craik vetoed this suggestion by Dr. Dick and continued to pursue bloodletting which was ineffective. Although tracheotomy would have likely saved his life, it was not performed, and at 10:20 pm that evening, George Washington, the first president of the United States of America, died with his wife Martha at his bedside (Fig. 66.3).

During the diphtheria epidemic of 1833, Pierre Bretonneau and his student Armand Trousseau were the first physicians

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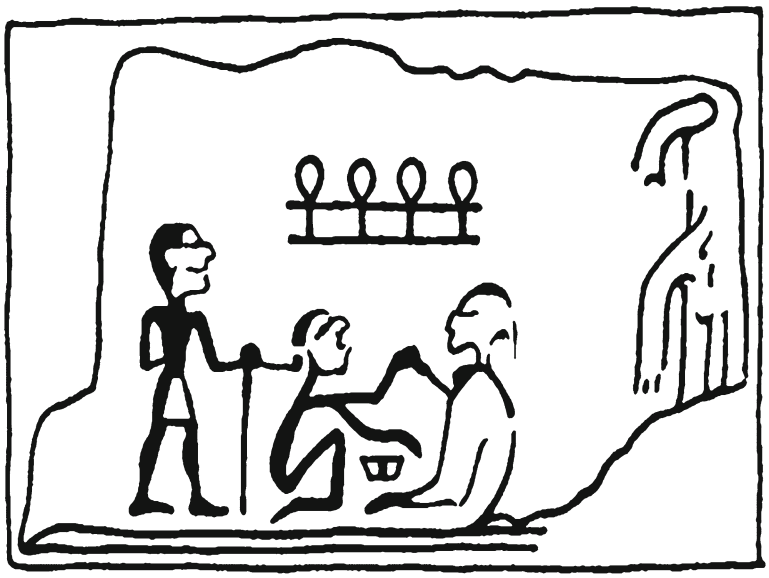

Fig. 66.1 King Aha Slab – 1st Dynasty (From Pahor AL. Ear nose and throat in Ancient Egypt. J Laryngol Otol. 1992;106:773–9. Courtesy of the Journal of Laryngology)

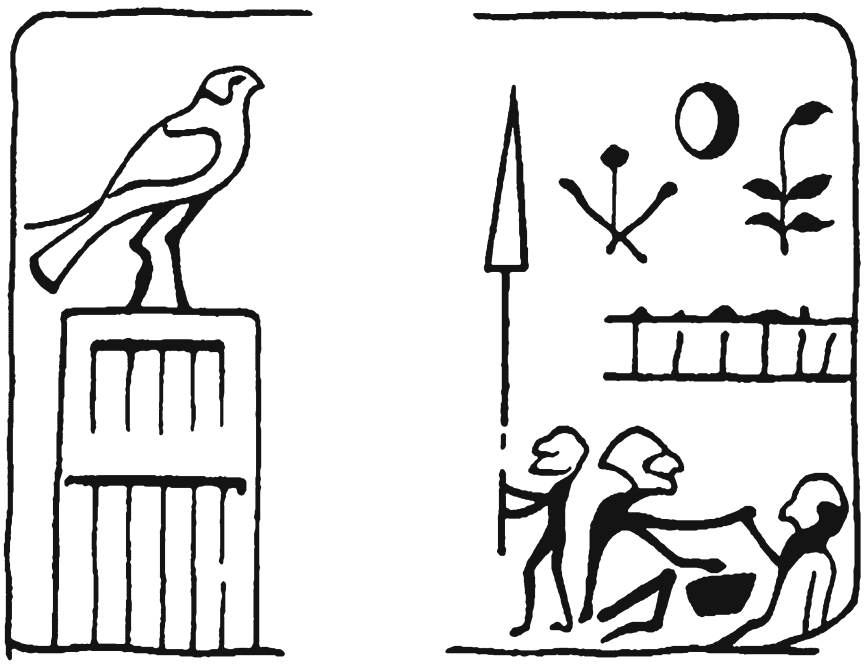

Fig. 66.2 Kind Dyer slab – 1st Dynasty (From Pahor AL. Ear nose and throat in Ancient Egypt. J Laryngol Otol. 1992;106:773–9. Courtesy of the Journal of Laryngology)

to document using tracheotomy on a routine basis. During this epidemic, Dr. Trousseau was quoted as stating, "Today gentleman, I have performed this operation more than 200 times and I am reasonable happy to have a success in more than 25% of cases." Trousseau was also the first to use a spreader to keep the trachea open during the procedure. In 1869, Trendelenburg developed the first cuffed tracheotomy tube, and although this was an improvement, due to its high operative mortality, tracheotomy continued to be used in limited circumstances at only a few institutions worldwide. The tracheotomy procedure further declined during the late 1800s. During that time, Dr. Joseph O'Dwyer joined the hospital staff at the Foundling Asylum of the Sisters of Charity in New York after completing his training at the College of Physicians and Surgeons in New York City. At that time, there continued to be a very high mortality of patients with laryngotracheal croup. From the period of 1869–1880, every patient who underwent a tracheotomy at the Foundling Asylum had died. Dr. O'Dwyer decided to make it his life's work to discover a treatment to prevent suffocation without surgical intervention and, as a result, pioneered the orotracheal tube. In 1894, he presented his data at the National Sciences Research Workers Meeting in Nuremberg that 40% of the 1,324 cases he had treated had fully recovered.

Fig. 66.3 The Death of Washington, Sketch from 1896 in Oil by Howard Pyle. Dr. James Craik is pictured standing, Dr. Gustavus Brown is seated, and Martha Washington sits at the foot of the bed (Courtesy of the Boston Public Library Print Department)

It was not until the early twentieth century that tracheotomy regained popularity due to the standardization of open surgical tracheotomy by the famous American surgeon Chevalier Jackson. Jackson is credited with reducing the operative mortality associated with tracheotomy at that time from 25% to 1%. He recognized and emphasized the importance of adequate oxygenation during the procedure as well as airway control. He also further advanced all surgical techniques by recognizing the importance of postoperative care. In the 1930s, tracheotomy was advocated as an effective way to provide bronchopulmonary toilet in patients with polio. Due to the continued modern track record of safety associated with the placement of tracheotomy tubes along with the widespread use of positive pressure ventilation in the 1950s, there was considerable effort focused on the development of tracheotomy tubes as a means of providing long-term ventilatory support.

In 1955, Shelden introduced the first modern-day percutaneous tracheotomy set which closely resembled the approach fist described by Sanctorius 500 years earlier. The procedure used a trocar over a needle that resulted in multiple deaths secondary to airway and vascular injury and was abandoned. In 1967, Toye and Weinstein first used the Seldinger technique to safely introduce a cannula into the tracheal lumen. The technique was further refined by Pasquale Ciaglia in 1985 in what has now become one of the most popular techniques for percutaneous dilatational tracheotomy (PDT).

Tracheal Anatomy

As with all invasive procedures, knowledge of the anatomy is an essential prerequisite prior to proceeding with any surgical procedure. Basic airway anatomy as well as a thorough understanding of the surrounding vasculature and vital structures which approximate the trachea is required. The trachea is a centrally located unpaired organ which extends in an oblique fashion from the superficial position in the neck and deeper into the mediastinum. The average length of the adult trachea is 11 cm (range 10–13 cm). Along the course of the trachea, there are 18–22 incomplete or semicartilaginous rings with an anteroposterior diameter of 1.8 and 2.3 cm in the lateral dimension. The cricoid cartilage in the larynx has the only complete cartilaginous ring and has a membranous attachment to the first tracheal ring. The posterior wall of the trachea or membranous trachea is comprised of a flexible sheet of fibroelastic tissue between the ends of the tracheal rings and abut the anterior portion of the esophagus. The combination of the rigidity of the anterior two-thirds of the trachea with the flexibility of the poster one-third allow for a great range of flexibility and stability to withstand the forces of forced expiration and coughing and allow continued airway patency.

There are several structures which lie anterior to the trachea which should be identified prior to tracheotomy. The thyroid isthmus is located between second and third tracheal rings, the innominate artery most often crosses the anterior trachea in an oblique fashion distal or inferior to the third tracheal ring and the aortic arch crosses above the carina. The recurrent laryngeal nerves lie in close proximity to the trachea within the tracheoesophageal groove. The blood supply to the cervical trachea enters posterolaterally from the inferior thyroid artery. As a result, when performing a tracheotomy, dissection along the anterolateral plane is safest to avoid vascular injury (Fig. 66.4).

Indication and Timing

Although there has been a significant reduction in tracheal injury secondary to endotracheal intubation, there are pros and cons related to each technique (Table 66.1).

In the 1960s, Drs. Hermes Grillo and Joel Cooper first reported tracheal injury due to cuffed endotracheal tubes.

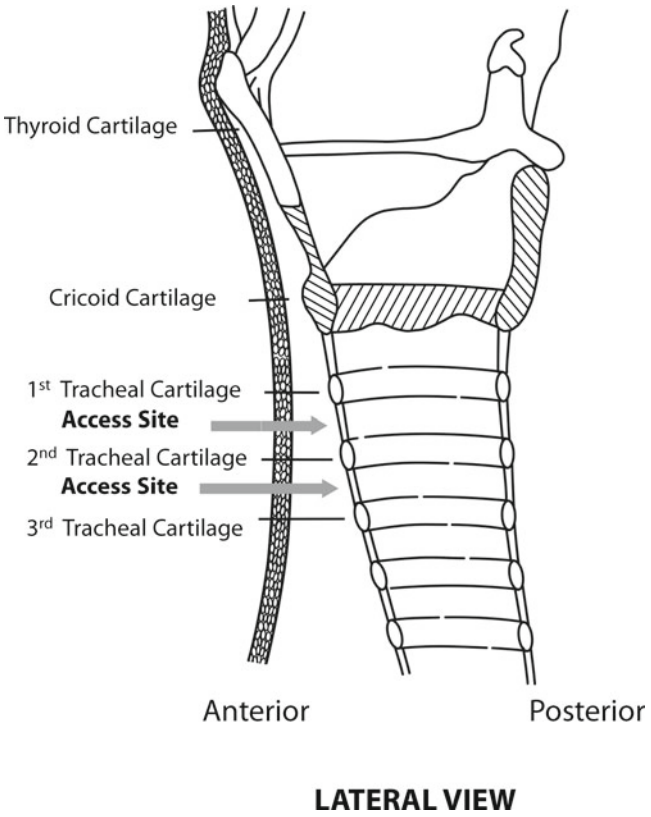

Fig. 66.4 Anatomic landmarks (Courtesy of Cook Critical Care, Bloomington, IN)

Table 66.1 Pros and cons of endotracheal tubes and tracheotomy tubes

	PROS	CONS
Tracheotomy tube	Decreased work of breathing	Potential loss of airway
	Decreased auto-PEEP	Tracheal stenosis at stoma
	Increased patient comfort	Tracheal stenosis/ malacia at cuff
	Decreased sedation	
	Facilitates transfer out of ICU	Surgical training needed
	Facilitates speech and swallowing	Surgical scar
	Facilitates airway suctioning	
	Increases patient mobility	
Endotracheal tube	Quickly reinserted under vision	Laryngeal injury
		Tracheal stenosis/ malacia at cuff
		Deeper sedation
		Requires ICU level of care

Since that time, high-volume, low-pressure, cuffs for endotracheal tubes have since been developed which resulted in a reduction in tracheal injury. Despite this reduction, there remains a significant degree of other complications including vocal cord injury, subglottic stenosis, and tracheomalacia (Fig. 66.5).

In addition, as more patients are ventilated for increasingly longer periods of time, there has been an associated increase in ventilator-associated pneumonia and mortality. Although tracheotomy can reduce some of these complications, the procedure itself has its own inherent complications, and as such, some studies recommend early tracheotomy as means of further reducing the additive effects of multiple procedures and the longer-term risks of prolong endotracheal intubation. The most recent 2001 American College of Chest Physicians guidelines for weaning and discontinuing ventilatory supports encourage early tracheotomy after patient stabilization if the patient needs prolonged mechanical ventilation more than 3 weeks after intubation where rates of ICU mortality and failure to wean increase. In the randomized controlled trial by Rumbak et al. comparing early (less than 48 h) versus late (14–16 days) tracheotomy in patients with respiratory failure, the early group had a significant decrease in mortality, pneumonia, and ventilator days. Terrangi et al. randomized 419 patients to receive early (6–8 days) vs. late (after 13–15 days) tracheotomy with a primary endpoint of incidence of ventilator-associated pneumonia and secondary endpoints of ventilator-free days, ICU-free days, and 28-day survival. There was a trend toward a decrease in VAP and a significant decrease in ICU days and successful weaning but no survival benefit. In a systematic review and meta-analysis by Dunham et al. comparing early versus late tracheotomy in trauma patients, there was benefit seen in the early tracheotomy group in ventilator days, ICU length of stay, and VAP only in the brain injury cohort.

To date, there are not enough well-designed studies to allow for a clear consensus or guidelines in regard to the timing of tracheotomy. Kollef et al. published a post hoc analysis of a prospective cohort study which found that patients who receive a tracheotomy have a lower mortality than those who do not, despite an increase in total days on mechanical ventilation and hospital length of stay. Although questions such as survival benefit and ventilator days remains in question, one must take into account other factors which have been established. Improved patient comfort, decreased need for sedatives, and increased ability to communicate with enhanced nursing care have all been shown to be improved by tracheotomy placement. Selection of patients who should undergo tracheotomy placement is a complex medical decision and as such needs to be individualized for each patient. Table 66.2 reviews suggested indications for PDT.

Contraindications

As with all procedures, the first major contraindication is the performance of the procedure by an inexperienced provider without appropriate supervision and guidance. The large

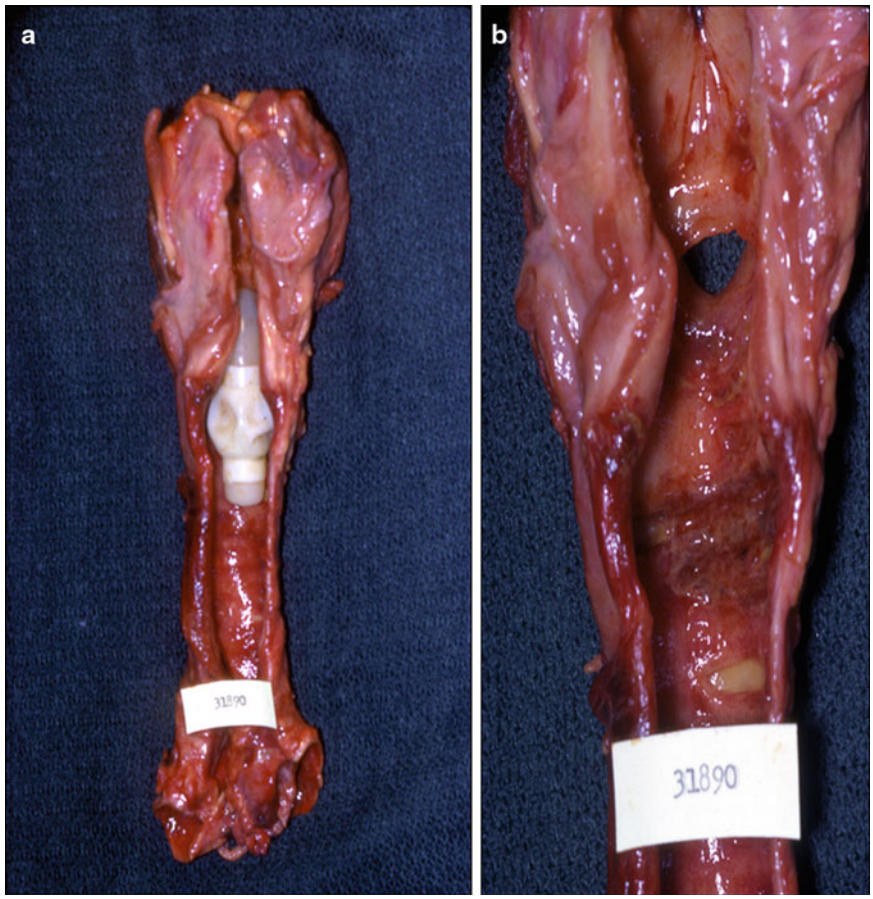

Fig. 66.5 (**a**) and (**b**) Tracheal injury where the cuff has caused some tracheal injury (8b) which is best seen with the tube removed (8c) from the autopsy specimen (Courtesy of Joel Cooper, M.D.)

Table 66.2 Suggested indications for PDT

Prolonged mechanical ventilation estimated or anticipated to be longer than 7 days
Enhancement of patient comfort prolonged weaning efforts
Failed extubation
Relief of upper airway obstruction
Secretion management
Need for bedside procedure secondary to increased risk of patient transfer to operating room

Table 66.3 Contraindications to PDT

Absolute
• Absence of informed consent
• Active site infection
• Uncorrectable bleeding diathesis
• Operator inexperience
• Infants
Relative
• Uncorrectable coagulopathy/thrombocytopenia
• Difficult airway
• Morbid obesity
• High ventilatory/positive end-expiratory pressure requirements
• Pediatric population
• Recent sternotomy
• History of neck surgery
• Emergent procedure

majority of PDT cases are elective, thus affording the proceduralist the luxury of performing a detailed history and physical examination to assess candidacy for bedside PDT (Table 66.3). Patients should be hemodynamically stable, and coagulopathy parameters should be corrected prior to proceeding with the procedure.

The neck anatomy should be carefully examined for high lying or crossing vasculature which greatly increases the risk of fistula formation. If these anatomic variants are identified, patients should be referred for open surgical tracheotomy to allow dissection and isolation of the surrounding vasculature. Ultrasound as a prescreening measure prior to PDT has been increasingly used in intensive care units. The use of an ultrasound probe with Doppler technology allows both a gross anatomic ultrasound examination, localization of the cartilaginous rings, and a vascular assessment that appears to reduce complications when used by a trained professional on a routine basis (Fig. 66.6). Although the overall risks during PDT are small, preoperative ultrasound assessment may further reduce these rare complications. In a study by Muhammad et al. where 497 PDT procedures were performed, six cases

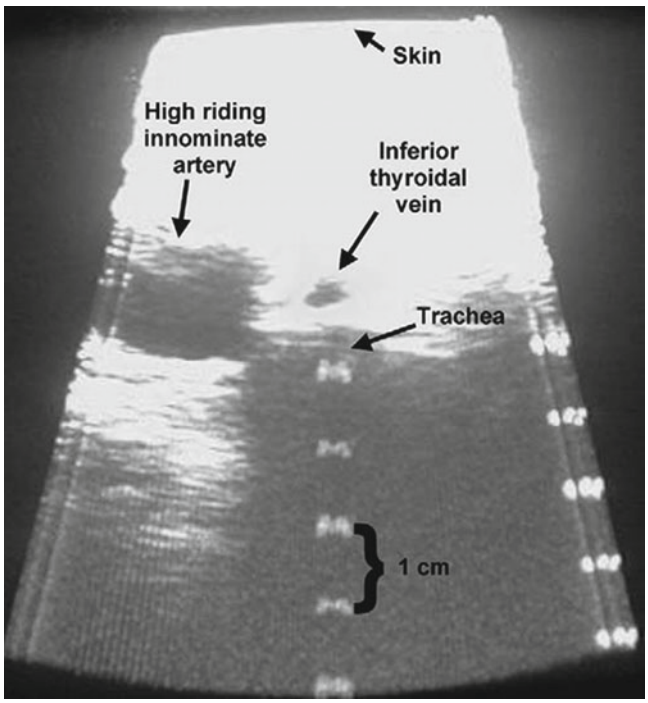

Fig. 66.6 Ultrasound of the base of the neck just cephalad to the sternal notch in an obese patient revealing a nonpalpable high-riding innominate artery and a large inferior thyroidal vein (Reprinted from deBouisblanc BP. Percutaneous dilational tracheostomy techniques. Clin Chest Med 2003;24(3):399–407. With permission from Elsevier)

were aborted due to bleeding, and 18 cases had clinically significant bleeding during the procedure (incidence of 4.8%). In a postprocedure review of these patients, 4 had ultrasound findings which could have identified the risk preoperatively (2 inferior thyroidal veins, 1 high brachiocephalic, and 1 aberrant anterior jugular communicating vein).

Additional contraindications include the presence of a significant infection or overlying cellulitis at the operative site. PDT in patients with cervical spine injury has been referenced as a relative contraindication but recently has been shown to be feasible and safe in a study from 2006 by Ben Nun et al. where 38 consecutive PDT procedures were performed on multitrauma patients with documented cervical spine fracture. All patients had successful and safe placement of a tracheotomy with a percutaneous approach by experienced operators. Recent neck or mediastinal surgery was previously considered a relative contraindication. Several recent studies have now shown that in experienced hands, PDT can safely and effectively be performed in postsurgical patients. Specifically, there is mounting evidence in the literature that there is no difference in outcomes between PDT and open surgical tracheotomy post-coronary artery bypass grafting surgery. Although studies suggest an increased risk for sternal wounds after tracheotomy and chest surgery, there does not appear to be a significant difference between the procedural technique used. Anatomic variations such as an overlying goiter, short neck, or difficulty with hyperextension secondary to underlying osteoarthritis may make the PDT approach more technically challenging but are a relative contraindication. PDT in the obese patient is also considered a relative contraindication and can be safely performed in experienced hands. This will be discussed in more detail later in this chapter. Although PDT has been shown to be performed safely in patients with hypoxic respiratory failure and high PEEP requirements, it should be done so only in the hands of experienced operators. In these patients, bronchoscopy did not jeopardize oxygenation in a large cohort study but has been shown to reduce the risk of perioperative complications and procedure time in a cohort study. In addition, the use of bronchoscopy will presumably also allow for better airway control in the event of bleeding or endotracheal extubation prior to the completion of the procedure.

Table 66.4 PDT preprocedure checklist

• Informed consent obtained
• Consent signed
• Laboratory and medication data reviewed
• Coagulopathy issues addressed
• Difficult airway assessment
• Reintubation equipment available
• Proper patient positioning
• Identification of anatomic landmarks
• Review of ventilator settings and oxygenation
• Preprocedure time put performed
• Initiation of universal precaution protocol

Preoperative Preparation

The use of the PDT technique has allowed for increasing numbers of tracheotomy procedures to be performed in the ICU which in turn has opened up operating room time for more technically challenging cases. However, it is critical that all patients considered for either open or percutaneous tracheotomy undergo the same pre- and perioperative evaluation and treatment to standardize the care of these patients. Centers should institute a program to standardize practice and thus limit complications.

At a minimum, centers performing bedside PDT should have a checklist available for the preprocedure assessment of patients. Table 66.4 is an example of a checklist used at a high-volume PDT center. With the increase in the number of bedside tracheostomies at our institution, we introduced a novel Percutaneous Tracheotomy Program in 2005. The program has since performed an average of 200 tracheostomies a year. The Johns Hopkins Percutaneous Tracheotomy Program is fairly unique in that it includes clinical support, a

research focus for academic endeavors, and administrative scheduling and database activities. With the PDT Program, we screen patients earlier and perform the procedure soon thereafter, promoting the comfort of the tracheotomy sooner than before the program's implementation. As a result, the Tracheotomy Program has decreased the length of stay in the ICU and the overall length of stay in the hospital. This decrease in the length of stay also has been noted in other ICU's that have instituted standardized programs.

In addition, tracheotomy teams can offer educational workshops to nurses and respiratory therapists to up-to-date ancillary staff on changes in protocols, policies, and practices. There are also academic advantages for a team approach in that data can be collected on all patients who undergo a percutaneous tracheotomy to create a database for study purposes with the hope of improving the PDT standards of care. This database can also serve as a quality assurance tool for the education of team members so that they might learn from their practice and experience. By performing tracheostomies earlier, and managing patients more efficiently with the help of the PDT Program, we have seen improvements in overall patient care with decreases in decannulation time, length of stay, and complications which in turn decrease the cost to patients and the health-care system.

The Percutaneous Tracheotomy Program at the Johns Hopkins Hospital was founded on the concept of a multidisciplinary approach of otolaryngology/head and neck surgery, anesthesiology, general/trauma surgery, and interventional pulmonology. Apart from the surgeons and anesthesiologists, the program service comprises a nurse practitioner (NP), a registered nurse, a respiratory care practitioner, speech-language pathologists, tracheotomy coordinators, and equipment specialists. Each member of the team performs a complementary role to provide state-of-the-art care to patients who undergo bedside PDT.l.

The standardized PDT Program encompasses a standardized surgical approach as well. The surgery is performed using the same tracheotomy kit (Cook Blue Rhino) under visual bronchoscopic guidance directed by the anesthesiologist. The anesthesiologists provide a safe perioperative environment during the percutaneous tracheotomy in the patient's room in the ICU. During the procedure, the anesthesiologist maintains a secure airway. The percutaneous tracheotomy NP is the overall multidisciplinary coordinator for the program. The NP screens patients who have been intubated for greater than 96 h, the threshold time period for consideration for a percutaneous airway. Should the idea of a tracheotomy be entertained by the ICU team, the percutaneous tracheotomy NP becomes a resource to the team and to the family, offering the time and expertise to explain the tracheotomy surgery, its associated risks and benefits, and to describe expectations following the procedure. In addition, The Hopkins PDT Program offers free educational resources to physicians and patients undergoing tracheotomy via the Web site www.hopkinsmedicine.org/tracheotomy.

PDT Kits

There are several PDT kits available in today's market. The operator should be well versed in the available techniques used to obtain tracheal access, but in general, it is recommended that the operator obtains competence using one technique initially based on their level of training. Currently, the Ciaglia Blue Rhino kit (Fig. 66.7) remains the most widely used PDT kit in North America. The Blue Rhino used a tapered dilator with a hydrophilic coating to allow single-step dilation. Other popular kits include the Ciaglia Blue Dolphin (Fig. 66.8) which utilizes a balloon dilatational technique, the Portex Uniperc Kit which is designed in a similar fashion to the Blue Rhino, the Portex Griggs forceps technique kit, and the Rusch Percutwist approach which uses a screw-like device to initiate the stoma. The PDT procedure

Fig. 66.7 Cook Blue Rhino PDT Kit (Courtesy of Cook Critical Care, Bloomington, IN)

Fig. 66.8 Cook Blue Dolphin PDT balloon dilation (Courtesy of Cook Critical Care, Bloomington, IN)

is described in more detail below for the Blue Rhino, Blue Dolphin, and the Uniperc Kits.

The two most popular kits for PDT are the Ciaglia Blue Rhino Percutaneous Tracheotomy Introducer Tray and the Portex Uniperc Kit. Both kits use a Seldinger technique followed by a single dilator for stomal entry and tracheotomy tube placement. The desired tracheotomy tube must be obtained separately or can be ordered with the introducer kit. Obese patients may require a tracheotomy tube with extra horizontal length which can be achieved by either technique. The Blue Dolphin also uses a modified Seldinger technique, but the dilation is performed in a single-step fashion with the tracheotomy tube preloaded potentially reducing procedure time. Although available on the market, the Portex Griggs forcep technique kit and the Rusch Percutwist approach have been largely replaced by the other techniques described above secondary to concerns for higher complication rates.

The PDT Procedure

One of the advantages of PDT is that the procedure can safely be performed at the ICU bedside. As discussed earlier, prior to committing to a bedside PDT, it is the operator's responsibility to perform a careful history and physical including review of the pertinent anatomy and laboratory data. Although studies have shown that PDT can safely be performed in the coagulopathic patient in experienced hands, we consider a PT/PTT < 1.5 times control and a platelet count >50,000/mm^3 acceptable. A retrospective study by Beiderlinden et al. showed that low-dose heparin treatment did not significantly increase the risk of chronic bleeding suggesting that if anticoagulation must be continued in patients on renal replacement therapy with associated low-dose heparinization, it is low risk to proceed with PDT. However, if heparin can be safely held, I suggest performing the procedure after a documented PT/PTT < 1.5. There have been no randomized studies reviewing the bleeding risk of patients on Clopidogrel, but given the presumed risk in the setting of an elective procedure, if patients have an absolute contraindication to holding Clopidogrel, I suggest they should be referred for surgical tracheotomy. Alternatively, if there is no contraindication to holding Clopidogrel, I suggest the medication be held 5–7 days prior to the procedure to allow normalization of platelet function. Although there are no trials reviewing the bleeding risk of Aspirin, anecdotally, there does not seem to be an increased risk, and as such, I do not hold aspirin prior to PDT. If the patient is uremic, we administer DDAVP prior to the incision. Given that PDT is an elective procedure, if there are multiple risk factors which may elevate the risk of complications during a bedside procedure, we generally refer high-risk patients for surgical tracheotomy.

Once the decision is made to proceed with PDT, we employ the multidisciplinary model discussed above. A detailed preoperative assessment is made by the NP on the tracheotomy team followed by a review of data and assessment by the anesthesiologist and operating surgeon. The anesthesiologist is positioned at the head of the bed with a free-flowing IV and airway management tools. Once consent is confirmed and a time out is performed, the patient is sedated and paralyzed by the anesthesiologist. An ICU nurse is charged with monitoring of vital signs, and a respiratory therapist preoxygenates the patient with an FiO_2 of 100% and controls the ventilator during the procedure with a backup rate as the patient will be paralyzed. A bronchoscopy is then performed with a therapeutic aspiration of any retained secretions prior to the start of the procedure. Hyperextension of the neck is then achieved by placing a rolled towel between the patients scapula which maximally increases the distance between the tracheal rings. The skin is then prepped with chlorhexidine, and a sterile field is created with a fenestrated drape. Anatomic landmarks are identified which include the thyroid cartilage, the cricothyroid membrane, the cricoid cartilage, and the tracheal rings as well as a palpation or ultrasound assessment for overlying vasculature (Fig. 66.9).

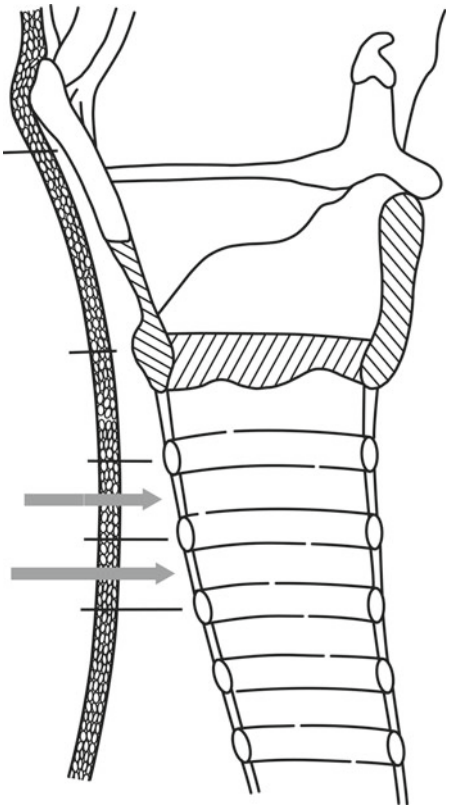

Fig. 66.9 Step 1 – Identifying landmarks (Courtesy of Cook Critical Care, Bloomington, IN)

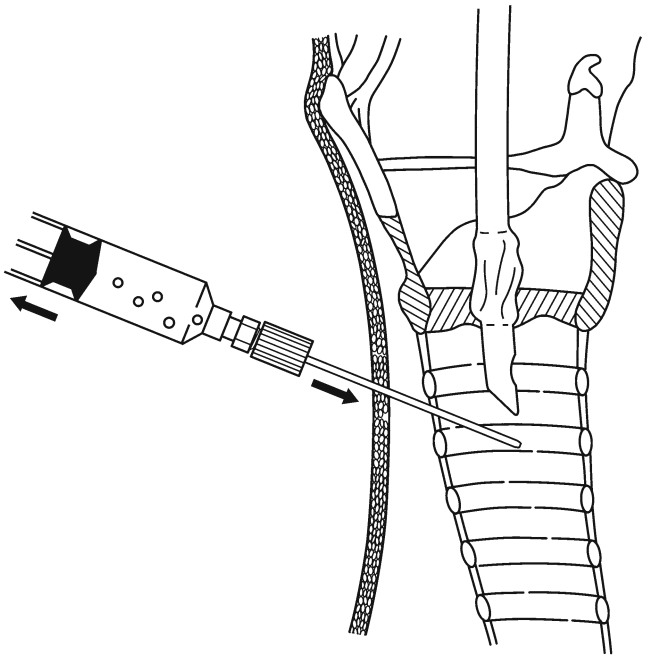

Fig. 66.10 Step 2 – Horizontal incision made followed by blunt mini-neck dissection and needle entry (Courtesy of Cook Critical Care, Bloomington, IN)

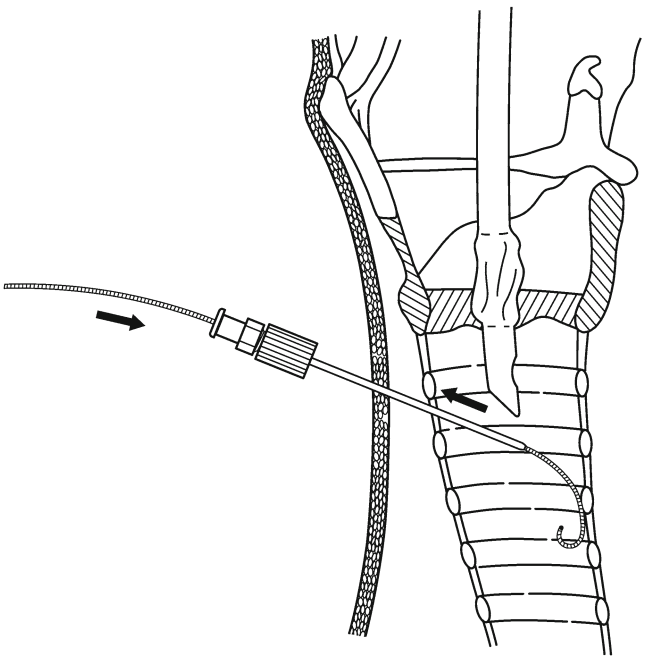

Fig. 66.11 Step 3 – Advancement of J wire into inferior trachea (Courtesy of Cook Critical Care, Bloomington, IN)

The preferred entry site is between the 1st and 2nd, or 2nd and 3rd tracheal rings. There are studies which recommend avoidance of the cricothyroid membrane to decrease the incidence of tracheal stenosis.

For the Blue Rhino, Blue Dolphin, and Portex Uniperc Kit, the initial steps are the same. The skin at the entry site should be infiltrated with up to 5 cc of 1.5% lidocaine with epinephrine. The epinephrine allows preferential vasoconstriction of the surrounding tissue to limit bleeding during the procedure. A 1.5-cm vertical incision is made through the skin and subcutaneous fascia, the soft tissue is bluntly dissected, and the tracheal rings are palpated. Our standardized approach at this point in the procedure has the anesthesiologist withdraw the endotracheal tube to lie just inferior to the vocal cords under both direct laryngoscopy and bronchoscopy visualization. Extra care is taken by the surgeon to be aware of the location of the bronchoscope to avoid scope puncture by the Seldinger needle. After bronchoscopic confirmation that the endotracheal tube lies superior to the stomal insertion site and transillumination is verified through the incision site, the tracheal rings are re-palpated, and the Seldinger needle is introduced into the midline trachea (Fig. 66.10).

The insertion angle of the introducer should be perpendicular to the trachea, and aspiration of air as well as direct bronchoscopic visualization confirms the proper location of the needle in the lumen of the trachea. A J-tipped guide wire is then advanced in the direction of the carina under vision and the needle is removed (Fig. 66.11). The tract is initially dilated with the short 14-French (Blue Rhino or Blue Dolphin

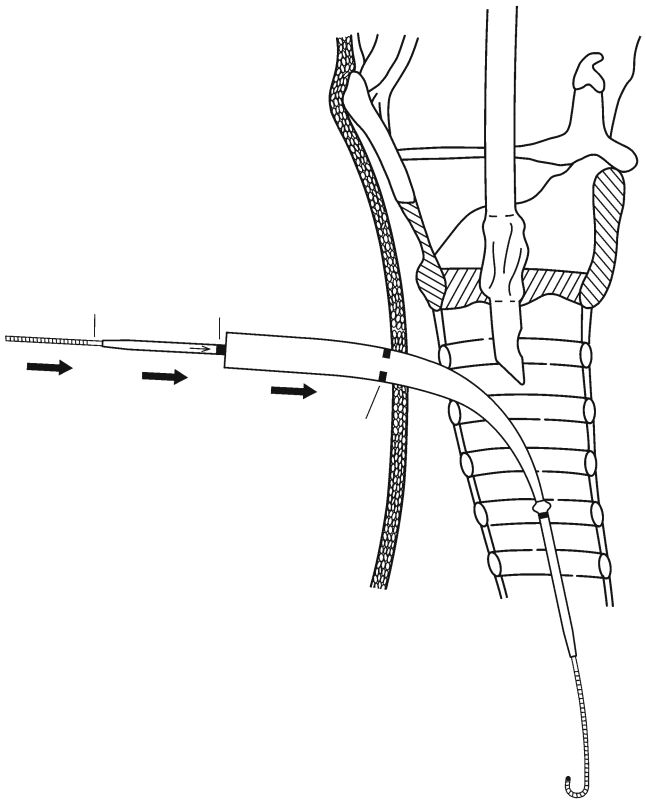

Fig. 66.12 Stomal dilation (Courtesy of Cook Critical Care, Bloomington, IN)

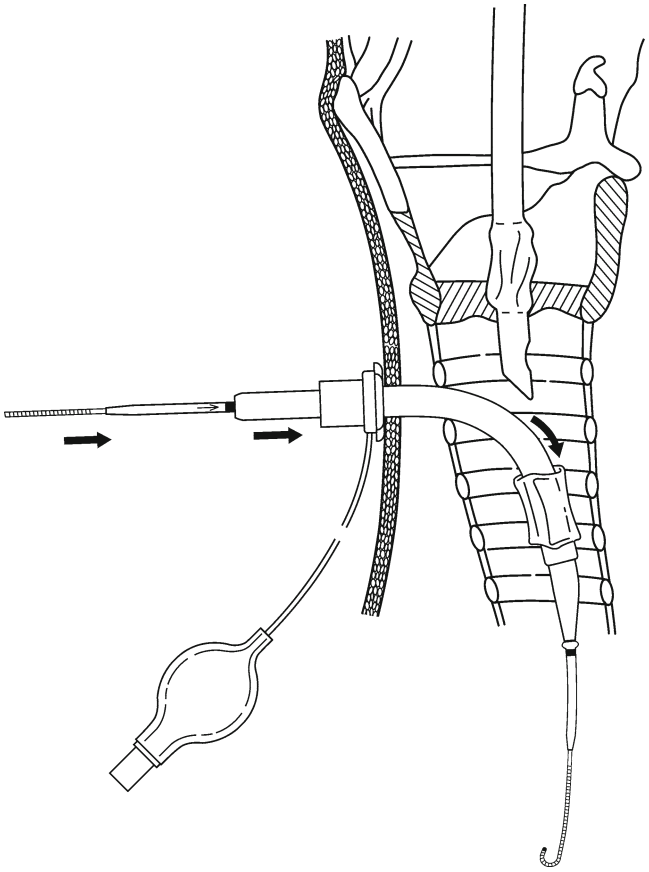

Fig. 66.13 Percutaneous placement of a tracheotomy tube (Courtesy of Cook Critical Care, Bloomington, IN)

Kit) or 10-French (Uniperc Kit) dilating (Fig. 66.12). This small dilator is then removed with the J wire remaining in place. The Blue Rhino and Uniperc Kits then use a single tapered dilator. The tracheotomy tube is then inserted on a separate obturator/dilator after the single taper dilator is removed, and the cuff is inflated (Fig. 66.13).

The Blue Dolphin uses a balloon dilatation method which combines the dilation step to the tracheotomy tube to eliminate one step in comparison to the Blue Rhino or Per Fit Kit. Although the Blue Dolphin technique eliminates a step during the PDT procedure, this does not translate to a deceased procedure time. A randomized study by Cianchi et al. compared the Blue Rhino technique to the Blue Dolphin technique and found that the Blue Rhino technique was shorter and associated with fewer minor tracheal injuries.

Adequate tube position is confirmed via bronchoscopy through the tracheotomy tube in addition to cuff inflation and return of tidal volume from the ventilator once the ventilator circuit is connected to the tracheotomy tube. After end tidal CO_2 is confirmed, a final bronchoscopic inspection through the tracheotomy tube is performed, and only then is the endotracheal tube removed. The tracheotomy tube is secured with suture or staples and a cloth tie such that one finger can be placed between the strap and the skin I secured. This is done at our institution to identify a freshly placed tracheotomy tube. It is our protocol that the operating surgeon performs the first tracheotomy change 10–14 days after initial insertions at which point the tie and suture/staple are removed and a Velcro tie is placed. This helps all staff to identify a fresh tracheotomy and prevent early removal prior to tract maturation. It is crucial during this step that one operator always hold the tracheotomy tube as it is being secured to avoid accidental decannulation. If this does occur, the patient should be re-intubated with a trans-laryngeal endotracheal tube with the cuff of the tube distal to the stoma. Attempts at tracheotomy tube reinsertion should only be done when the airway is secure, and as the tract is immature, the introducer needle and guide wire should be used to avoid misplacement into the mediastinum. Postoperatively, given the use of bronchoscopic guidance and visual confirmation, we do not perform a routine chest radiograph. A study by Kumar et al. prospectively reviewed 345 PDT procedures with a postoperative chest radiograph and found that it did not reveal any unexpected radiographic abnormalities.

Surgical Versus Percutaneous Tracheotomy

Multiple well-designed randomized controlled trials and meta-analyses comparing PDT and surgical tracheotomy (ST) have been studied. The most recent or significant trials will be reviewed here.

Elective tracheotomy in the ICU performed at the bedside using the PDT technique offers several advantages over ST. In general, there are limited complications of bedside PDT in the ICU which either compare or are less than those associated with surgical tracheotomy performed either in the operating room or at the bedside. Using the PDT approach, there is less clinically significant wound infections observed most likely due to the limited tissue manipulation when compared to ST. Most studies have shown there is no significant difference in bleeding risk between PDT and ST. A randomized controlled trial with long-term follow-up by Silvester showed no difference in short- or long-term complications between the groups. In a recent study by Seder et al. clinical outcomes of PDT performed by neurointensivists versus ST were compared retrospectively with no significant difference in complications and a significant cost savings in the PDT arm. In a large study, Moe et al. found an overall procedure-related mortality rate of only 0.4%, major hemorrhage and pneumothorax occurred in 0.6%, wound infection in 0.8%, paratracheal insertion in 0–6%, accidental decannulation in 0–2%, and minor hemorrhage in up to 3% with no significant difference in surgical approach. A meta-analysis of 115 patients undergoing PDT and 121 ST by Freeman et al. found no significant difference in the overall operative complication rate. PDT in this study was associated with a small reduction in operative bleeding, and postoperative complications were significantly less common in the PDT group. The study also confirmed the reduced procedural time of PDT compared with ST (20.1 min vs. 41.7 min) and also found that PDT charges were significantly less ($1,569 vs. $3,172), though the majority of this savings was due to the lack of OR charges associated with PDT. Although most studies quote a time advantage favoring PDT, it is likely the majority of time savings is due to decreased patient preparation time. Although this is no clinical significance from a procedural standpoint, it does factor into cost savings and operating time budgetary considerations. The question as to whether performing tracheotomy at the bedside will limit the risk of patient transportation has been studied. Massick et al. randomized 100 patients to PDT or ST performed at the bedside in the ICU and compared the results to an additional 64 patients who had ST performed in the OR [6]. The incidence of postoperative complications did not differ between the bedside and OR groups.

Tracheal stenosis has been shown to occur after both endotracheal intubation and tracheotomy with an incidence of clinically significant tracheal stenosis estimated at 1.8%. This stenosis can occur at the level of the tracheal stoma or at the level of the cuff of the endotracheal/tracheotomy tube. As almost all patients with tracheotomy tubes have previously had an endotracheal tube in place, it can be difficult to identify the causal factor, unless the stenosis is at the level of the stoma. In a study by Stoeckli et al. comparing patients who underwent both PDT and ST, laryngotracheal specimens were collected from 21 patients who had died, and although PDT was associated with a higher incidence of cartilage fractures at the introduction site, none of the patients in either group developed clinically significant tracheal stenosis. Table 66.5 reviews the complications associated with tracheotomy.

Table 66.5 Complications of tracheotomy

Acute
• Aspiration pneumonia
• Tracheal ring rupture or herniation
• False lumen insertion
• Unplanned extubation
• Pneumothorax
• Pneumomediastinum
• Tracheal wall laceration
• Bleeding
• Local site or deep infection
• Cardiac arrest
Delayed
• Tracheoinnominate artery fistula
• Tracheoesophageal or tracheoinnominate artery fistula
• Mucus impaction
• Cellulitis
• Ventilator-associated pneumonia
• Aspiration (inadequate cuff pressures)
• Mucosal wall ischemia/necrosis (related to high cuff pressure)
• Granulation tissue formation
• Tracheomalacia
• Post-tracheotomy tracheal stenosis

Bronchoscopy During PDT

The use of bronchoscopic visualization during PDT has been proposed as a method to reduce the complication rates during PDT. These benefits include ensuring midline placement of the needle and guide wire, safe withdrawal of the endotracheal tube, and avoidance of paratracheal placement or injury to the posterior tracheal wall. Potential complications associated with the use of bronchoscopy during PDT include hypercapnia and damage to the bronchoscope from the introducer needle. To date, there are no randomized trials comparing the use of the bronchoscope during PDT. A study using bronchoscopic visualization during PDT in obese critically ill patients showed no difference in the procedure

performed in standard patients with bronchoscopic visualization suggesting a safety benefit in this subset population. We suggest the use of bronchoscopy during PDT for the reasons above, but further studies are needed to better define its role in PDT.

Repeat Tracheotomy with PDT

Initially, the PDT technique was thought to be a contraindication for patients requiring a new tracheotomy. This issue was first addressed by Meyer et al. by reviewing 14 consecutive patients who had undergone a previous tracheotomy between 8 days and 10 years before the repeat procedure. All patients subsequently underwent PDT for the repeat procedure with the incision made at the site of the initial scar. There were no periprocedural complications in this group. In a similar study by Yilmaz, PDT was used for patients who needed repeat tracheotomy in a neurocritical care unit. Twelve consecutive patients (mean age 35.4 +/− 7.0 years) who underwent repeat percutaneous tracheotomy had a repeat tracheotomy tube placement with PDT, and all were successful with none of the patients needed conversion to surgical tracheotomy. These reports suggest that prior tracheotomy should not be used as definitive exclusion criteria for PDT.

PDT in the Obese Patient

Morbid obesity can make PDT technically more challenging. Obscuration of anatomic landmarks, increased depth of predilatation dissection, and limited customized tubes readily available can make the procedure difficult. However, it has been shown that in experienced hands with adequate preparation, PDT can be performed safely and effectively in obese patients. In this case series by Mansharamani et al. 13 patients who were consecutively referred for PDT and were obese (body mass index >27 kg/m^2) underwent bedside PDT. All 13 patients had successful placement of a bedside tracheotomy using the PDT approach. One patient had an initial paratracheal placement which was identified and corrected prior to endotracheal extubation. There was no serious bleeding or cardiopulmonary complications during the procedure. The operators in this series had significant experience with tracheotomy performing over 400 PDTs at the bedside. A retrospective review of 1,062 tracheostomies was performed at a single institution over 4 years by Heyrosa and colleagues. 135 of these patients had a BMI >35 of which 89 underwent PDT and 53 ST. There were no complication differences between PDT and ST in morbidly obese patients in this study which reviewed hypoxia, bleeding requiring surgical interventions, or malplacement of the tracheotomy tube. In experienced hand, PDT can be performed safely at the bedside in obese patients. Extra planning is critical in this patient population, and the operator should have multiple tracheotomy tubes available to ensure the most appropriate sizing and fit.

Credentialing

PDT is a relatively simple procedure and has an excellent track record of safely being performed at the ICU bedside by proceduralists who have not had formal surgical training. Regardless of the subspecialty, the operator should first and foremost be appropriately trained in advanced airway management including emergent airway techniques. Formal training prior to performing PDT is essential and should begin with hands-on instruction by an expert, and supervision by an experienced operator is encouraged especially when performing the first several cases. Although complications are rare, a multidisciplinary team is strongly encouraged when embarking on starting a PDT Program to aid in the necessary communication and collaboration between subspecialists if and when complications occur. The most recent guidelines published by the American College of Chest Physicians suggest that 20 supervised procedures, followed by at least 10 per year are required in order to perform and maintain competency in PDT.

Summary

PDT has rapidly become one of the most commonly performed procedures in the ICU. It has been shown to be both safe and efficient procedure in the ICU. In addition, the cost-effective aspect of the procedure when compared to surgical tracheotomy may be favorable. Appropriate patient screening and preprocedure planning are important aspects surrounding a successful PDT Program. As with any procedure, it should be performed by experienced personnel with additional expertise in airway management. Although additional studies are needed to refine the best PDT technique, there is adequate data to support the findings that the PDT approach is comparable to traditional ST.

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Cricothyroidotomy

67

Joshua B. Silverman

Introduction

Cricothyroidotomy is the quickest and safest procedure to obtain an adequate airway in a patient in whom intubation has failed. Cricothyroidotomy is the creation of a surgical opening through the cricothyroid membrane and placement of a tube for ventilation. This differs from tracheostomy in which a lower opening is made through the anterior tracheal wall and a tube is placed in a different anatomic location. Tracheostomy, while still preferred for long-term airway management, has a higher complication rate than cricothyroidotomy when performed on an emergent basis and thus should be performed in a more controlled setting.

Early control of the airway is one of only a few interventions shown to improve outcome for severely injured patients. These patients often present with a difficult airway, a scenario which has been defined by the American Society of Anesthesiologists in their practice guidelines. A difficult airway is "the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with face mask ventilation, difficulty with tracheal intubation, or both" (2003). Factors that can lead to inability for successful intubation include difficult patient anatomy; airway obstruction due to angioedema, trauma, burns, or foreign body; excessive bleeding; or facial trauma.

The surgical airway remains the final common pathway on all difficult airway algorithms, and cricothyroidotomy is an effective technique if emergency invasive airway access is required. Cricothyroidotomy is standardly taught in advanced life support classes (ALCS), and the majority of emergency cricothyroidotomy is performed in the prehospital setting due to immediate airway obstruction secondary to trauma. In the hospital setting, a difficult airway patient may be managed by a multidisciplinary airway team consisting of anesthesiologists, otolaryngologists, pulmonologists, general surgeons, and emergency physicians. Each of these physicians should be trained in cricothyroidotomy.

This chapter will explore the history of cricothyroidotomy, relevant anatomy, and indications for this procedure. We will describe different techniques for cricothyroidotomy as well as postoperative considerations and potential complications.

Historical Perspective

Creation of a surgical airway as a lifesaving procedure was first described more than 5,000 years ago on Egyptian tablets. Tracheostomy was described by Galen in the second century of the Common Era, and Vesalius published a detailed description of this procedure in the sixteenth century, though his resuscitation of a Spanish nobleman using this technique was condemned by the Spanish Inquisition, leading to his banishment. An Annals of Surgery article from 1886 by Colles described a 50% mortality rate for tracheostomy, and subsequent airway stenosis was commonly found. Many physicians in the nineteenth and early twentieth century were reluctant to perform tracheostomy due to a high complication rate.

In 1909, Chevalier Jackson delivered a landmark speech on tracheostomy at a meeting of otolaryngology physicians in which he described tracheostomy as a safe and effective procedure and outlined principles that continue to be relevant today. He quoted his own mortality rate as four patients of 100 who underwent tracheostomy. Jackson implored other physicians to perform the procedure at first indication of airway obstruction, rather than wait until a patient was unable to adequately ventilate, as he noted that surgical performance is improved in a more controlled setting. He cautioned against the use of sedation for patients in respiratory distress and recommended multiple methods still used today to avoid complications: repeated palpation of the trachea in the

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midline during surgery, meticulous hemostasis, and vigilant postoperative care.

Jackson's techniques became widely accepted, as did his aversion to the high tracheostomy, the original term for cricothyroidotomy. In another paper in 1921, Jackson presented retrospective results of 200 patients referred to his clinic for chronic laryngeal stenosis. Most patients presented with upper airway obstruction secondary to inflammatory or infectious lesions. After eliminating patients with stenosis seemingly caused by infectious processes alone, he determined that 93% of the remaining 170 patients had undergone high tracheostomy, during which the cricoid cartilage had been divided. He strongly warned against this practice, and his instructions were generally followed by the medical community for over 50 years. Though Jackson was probably correct in his assumption that the original technique used during high tracheostomy did contribute to chronic laryngeal stenosis, the underlying etiology of upper airway obstruction also contributed.

Even though the most common causes of airway obstruction changed during the twentieth century, cricothyroidotomy was not commonly performed due to concern for postoperative stenosis. However, in 1976, Brantigan and Grow, both cardiothoracic surgeons, published a large retrospective series of 655 patients who had undergone cricothyroidotomy. The authors became interested in the procedure to prevent contamination of the median sternotomy incision from the airway incision. Importantly, in contrast to the traditional high tracheostomy, only the cricothyroid membrane was incised to cannulate the airway. In their series, the rate of stenosis was very small, with very few complications. Brantigan and Grow presented cricothyroidotomy as an alternative to tracheostomy even for elective cases and did not convert from cricothyroidotomy to tracheostomy. In the following years, multiple studies confirmed that cricothyroidotomy can be safe and effective. Recently, studies have shown that this procedure can be successfully performed by various medical specialists and nonphysician health-care workers, both in the hospital and the field.

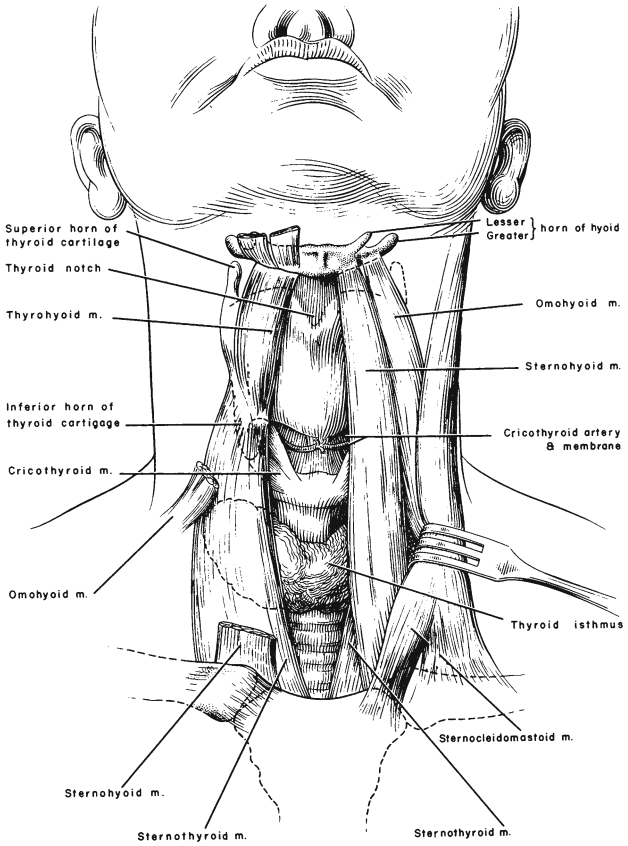

Fig. 67.1 Anterior neck landmarks for cricothyroidotomy (From Montgomery W. Surgery of the Larynx, Trachea and Esophagus. Philadelphia: Elsevier; 2002, p. 261. Reprinted with permission from Elsevier)

Relevant Anatomy

Since cricothyroidotomy is most frequently an emergent procedure, a thorough understanding of relevant anatomy is necessary for successful airway stabilization while avoiding complication. Multiple authors have suggested that understanding anterior neck anatomy contributes to speed and success of cricothyroidotomy. The most easily palpable anterior landmark is the thyroid notch, particularly in men. By sliding a finger down the thyroid cartilage, the cricothyroid membrane can be identified just inferior to the border of this cartilage and superior to the cricoid cartilage (Fig. 67.1). At the level of the CT membrane, only subcutaneous fat and the anterior cervical fascia separate the skin from airway, providing a simple surgical route to airway cannulation. However, in patients with significant neck edema or trauma, or in obese patients, landmarks may not be palpable. An alternative landmark is the suprasternal notch, which is typically three to four fingerbreadths below the CT membrane with the neck in neutral position.

The CT membrane or ligament connects the cricoid to the thyroid cartilages. It is located anterior to the cricothyroid articulation, and it extends superiorly deep to the thyroid cartilage as the conus elasticus within the subglottic region. The CT membrane is covered anterolaterally by the cricothyroid muscles. Approximate dimensions of the CT membrane are 10 mm in height and 22–33 mm in width. On average, 8 mm separates the medial borders of the cricothyroid muscles in the midline; this is the ideal area for cricothyroidotomy. There are no major arteries, veins, or nerves in the central portion of the CT membrane. The cricothyroid artery typically arises from the superior thyroid artery, with right and left cricothyroid arteries frequently traversing the superior

half of the CT membrane, giving off small branches that penetrate the membrane. For this reason, incision within the CT membrane should be made in the lower half. The two cricothyroid arteries may anastomose in the midline and then descend to supply the pyramidal lobe of the thyroid gland. However, even if one of these small arteries is encountered during the procedure, bleeding can usually be controlled with direct pressure.

The anatomical structures around the CT membrane are typically far enough away that they are not encountered during cricothyroidotomy. The vocal folds are located approximately 10 mm above the superior aspect of the CT membrane, and as long as a ventilation tube is directed downward when advanced through the membrane, injury to the vocal folds is not expected. The thyroid gland isthmus lies anterior to the trachea between the second and fourth tracheal rings, usually below the level of dissection for cricothyroidotomy. As the trachea descends caudally, it travels posteriorly as well, one reason that anterior access to the trachea may be more difficult during tracheostomy. Also, as tracheostomy is typically performed at the level of second to fourth rings, hemorrhage from the thyroid gland itself or vessels surrounding the gland is more concerning during tracheostomy than cricothyroidotomy. The carotid arteries and internal jugular veins lie posterolateral to the cricoid cartilage, and strap muscles can function as an easily identifiable lateral border of dissection. Anterior jugular veins can be avoided by making a vertical incision in the skin and staying in the midline during the procedure. Finally, risk of injury to recurrent laryngeal nerves is low, as these structures also lay posterolateral to the anterior laryngotracheal complex.

Indications and Contraindications for Cricothyroidotomy

The primary indication for an emergent surgical airway is the failure of endotracheal intubation or noninvasive airway maneuvers in a patient requiring immediate airway control. The 2003 American Society of Anesthesiologists consensus statement confirms surgical airway as the endpoint for unsuccessful airway control in an emergency setting. As soon as an inability to intubate and ventilate is determined, surgical airway access should be pursued; continued attempts at intubation increases morbidity and mortality.

Cricothyroidotomy can also be used as a primary attempt at securing the airway in cases of severe trauma. It can be performed safely in patients with cervicothoracic spinal injuries in whom tracheostomy cannot be done and has become useful in patients undergoing extensive maxillofacial surgery. As either a primary or secondary procedure, cricothyroidotomy is used for the immediate relief of upper airway obstruction. The etiology of the obstruction can be trauma; edema from infection, allergy, or burn; foreign body; laryngeal stenosis; or extrinsic compression.

Some authors advocate cricothyroidotomy as an alternative to tracheostomy for elective airway management. The primary argument against elective cricothyroidotomy was increased incidence of subglottic stenosis, as championed by Jackson in the early twentieth century. However, when Brantigan and Grow began to use cricothyroidotomy in order to maintain greater distance between their surgical airway and median sternotomy incisions to protect against wound contamination, their initial report in 1976 showed no cases of chronic subglottic stenosis, in direct contrast to Jackson's work. Though follow-up work published by the same authors 6 years later did identify patients with airway stenosis (17 of 655 patients), the subset was small compared to the number of cricothyroidotomies performed. They cited three predisposing factors: prolonged endotracheal intubation, vocal fold paralysis, and history of laryngeal trauma.

Cricothyroidotomy for long-term airway access was also prospectively studied in 76 patients by Sise et al. in 1984. Five patients developed major complications, including three with subglottic stenosis, and one patient died due to loss of the airway during the procedure. Autopsies were performed on many of the patients who died during the study period still with their cricothyroidotomy in place, and 28% had pathologic laryngeal changes. In analyzing these results, the authors suggested that elective long-term airway access could be achieved by cricothyroidotomy or tracheostomy with similar potential morbidity and mortality, though the former procedure is easier to perform.

More recently, a subset of trauma patients were retrospectively studied who had undergone elective cricothyroidotomy due to challenging neck anatomy. A surgical airway was indicated for anticipated prolonged ventilator dependence, and all patients were already intubated at the time of cricothyroidotomy. Rehm and coauthors reported an acceptably small complication rate and recommended the procedure as an alternative in these patients with obscured anatomical landmarks.

However, contradictory data suggest that cricothyroidotomy should be used sparingly as an elective procedure. Weymuller and Cummings aborted their comparative study between elective cricothyroidotomy and tracheostomy due to a very high complication rate (40%) in cricothyroidotomy patients with antecedent endotracheal intubation. They concluded that prolonged intubation is a contraindication to cricothyroidotomy due to acute laryngeal inflammation from the endotracheal tube. Similarly, Cole and Aguilar concluded that cricothyroidotomy must be avoided in any patient with laryngeal pathology. Intubation causes laryngeal inflammation and mucosal trauma, and the risk of chronic subglottic stenosis significantly increases in patients undergoing cricothyroidotomy following prolonged intubation. Based on these

studies and others, it is advisable to avoid cricothyroidotomy as an elective procedure in patients intubated for longer than 5–7 days, if laryngeal inflammation or infection is present, or there is history of laryngeal trauma.

A strong contraindication to surgical cricothyroidotomy is age less than 10 years. The CT membrane in a child is disproportionately smaller than in an adult, prior to laryngeal descent in the neck and cricoid expansion. In an infant, the width of the membrane makes up only one-fourth of the anterior tracheal diameter, as compared to three-fourths in an adult. Due to more obscured landmarks and this smaller membrane area, cricothyroidotomy becomes very difficult in children. Instead, needle cricothyroidotomy with percutaneous transtracheal ventilation should be the procedure of choice in this age group.

Relative contraindications for surgical cricothyroidotomy include severe neck trauma or edema and expanding neck hematoma. In these situations, landmarks may be obscured, and the anatomy may be significantly distorted, making cricothyroidotomy difficult. Known upper tracheal pathology is another relative contraindication. If a true anatomic barrier exists, then a lower tracheostomy may be the only viable option to secure the airway. However, even malignancy becomes a distant secondary concern if the situation demands immediate action to procure an airway. It should be noted that emergency tracheostomy or the so-called slash trach does carry a higher risk of complication than cricothyroidotomy.

Cricothyroidotomy Techniques

Needle Cricothyroidotomy

In needle cricothyroidotomy, a catheter is placed over a needle that penetrates the CT membrane, allowing ventilation by a pressurized stream of oxygen (Fig. 67.2). In adults, the catheter is usually too small to provide adequate ventilation other than as a temporizing measure; typically, needle cricothyroidotomy is only used in preparation for either surgical cricothyroidotomy or tracheostomy. Though oxygen can be delivered by this method, there is limited ability to actively eliminate carbon dioxide.

In children younger than 10–12 years, needle cricothyroidotomy is the preferred method for establishing an emergency airway, since the CT membrane is small and can be difficult to locate quickly. Surgical cricothyroidotomy may easily damage the larynx in this age group, with a higher incidence of postoperative airway complications. In young children, needle cricothyroidotomy should be converted to tracheostomy as soon as feasible.

A large bore needle with catheter (e.g., 14 gauge) attached to a syringe partially filled with water or saline should be immediately accessible in any potential difficult airway situation. Palpation of midline landmarks should allow identification of the space between the thyroid and cricoid cartilages. The needle with attached syringe is advanced through the skin at a 45 ° angle pointing inferiorly. When the needle pushes through the CT membrane, aspiration will reveal air bubbles within the syringe. The needle is withdrawn, leaving the cannula in place. Oxygen tubing is then connected to the cannula, and oxygen can be delivered at a high flow rate of 10–12 l per minute. Use of a Y-connector will allow periodic release of some carbon dioxide.

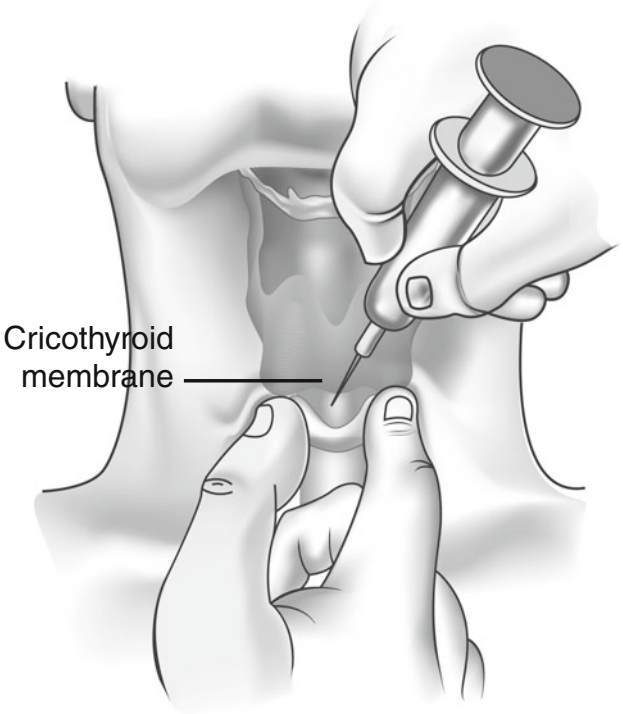

Fig. 67.2 Needle cricothyroidotomy

Surgical Cricothyroidotomy

Equipment should be easily accessible and bundled together, avoiding delay. Suggested supplies are listed in Table 67.1. Surgical cricothyroidotomy is performed as follows (Fig. 67.3a–d):

A. Neck Preparation, Positioning, and Landmark Identification

Sterile technique should be observed as much as possible with the application of and appropriate antiseptic solution to the patient's anterior neck, from the angle of mandible to sternal notch (Fig. 67.3a). Positioning for cricothyroidotomy

differs than that for tracheostomy, as it is more important for the patient's mandible to be anteriorly displaced than for the neck to be extended, as in tracheostomy. Palpation and identification of external landmarks including thyroid cartilage, cricoid cartilage, and sternal notch is a critical first step. Using the nondominant hand and standing to the right side of the patient, the larynx is firmly immobilized by the thumb and long finger, with the index finger free to palpate, locate, and reidentify the cricothyroid (CT) membrane at anytime during the procedure.

B. Skin and CT Membrane Incisions

With the operator's dominant hand, a 2-cm midline vertical skin incision centered over the CT membrane is made, avoiding injury to the anterior jugular veins (Fig. 67.3b). The incision should go through skin and subcutaneous tissue down to the level of the thyroid and cricoid cartilages. Then, with the left hand still pinning the larynx in midline, the index finger palpates the CT membrane through the incision, reconfirming its position and planning the following steps. After the CT membrane is carefully localized through the wound, a horizontal incision through the lower border is attempted to avoid injury to the superiorly positioned cricothyroid artery and vein.

Table 67.1 Equipment for emergency cricothyroidotomy

Scalpel with no. 15 blade
Hemostats ×2
Cricoid hook
14-g needle with cannula, 6-cc syringe with saline
Trousseau dilator or Kelley clamp
Cuffed no.4 tracheostomy tube (previously tested cuff)
Cuffed no. 5 endotracheal tube (previously tested cuff)
Gauze
Betadine, surgical drapes

C. Exposure and Dilation of CT Membrane Opening

After the CT membrane incision, a cricoid hook is inserted through the incision to the upper aspect of the cricoid cartilage, and gentle upward traction is applied, bringing the airway closer to the skin (Fig. 67.3c). Though traditional teaching describes traction on the inferior aspect of the thyroid cartilage, we prefer to hook the cricoid so that injury to the vocal folds is avoided. Next, a Trousseau dilator or a Kelly clamp is inserted through the CT membrane incision and spread in a cephalocaudal direction to enlarge the airway opening.

D. Insertion of an Appropriate Cannula

At this point, a tracheostomy tube or endotracheal tube should have been previously tested and available on the

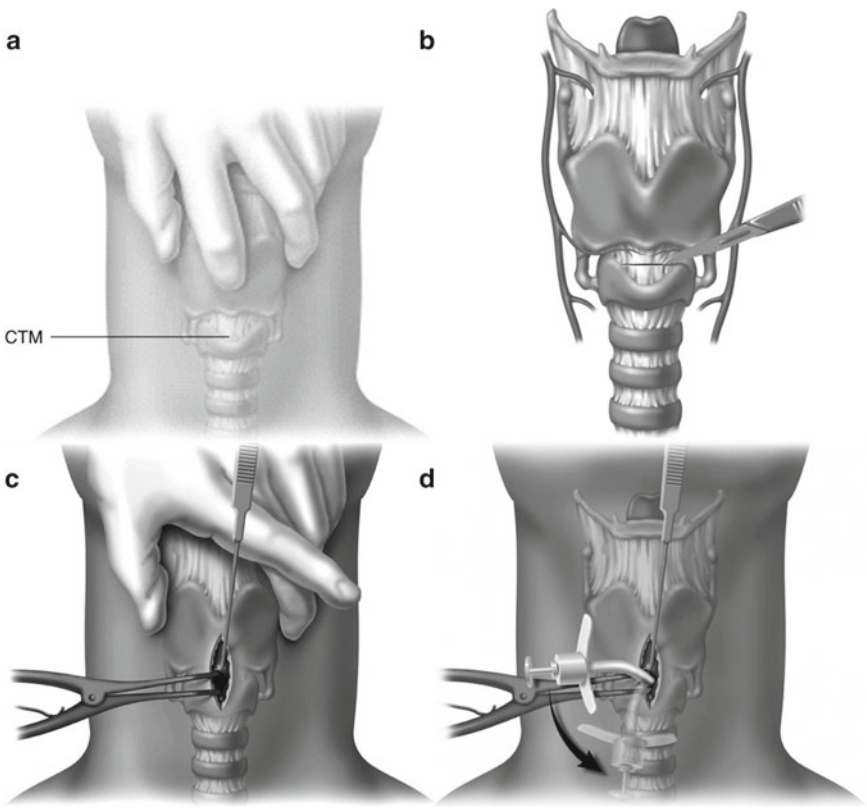

Fig. 67.3 Technique for surgical cricothyroidotomy. (**a**) Neck preparation, positioning, and landmark identification. (**b**) Skin and cricothyroid membrane incisions. (**c**) Exposure and dilation of cricothyroid membrane opening. (**d**) Insertion of an appropriate cannula (From Hagberg CA. Surgical airway. In: Benumof's Airway Management. Philadelphia: Elsevier; 2007; p. 686–90. Reprinted with permission from Elsevier)

surgical field (Fig. 67.3d). With the dilator still in place, insertion of the cannula is done between the dilator blades at a 90 ° angle. Counterclockwise rotation will seat the tube firmly against the patient's anterior neck. The size of the tracheostomy or endotracheal tube should not exceed an outer diameter of 8 mm, given the dimensions of the cricothyroid membrane. Before the tube is fixed to the neck with suture, proper placement should be confirmed by both the presence of CO_2 return on the monitoring equipment and successful auscultation of breath sounds.

Rapid 4-Step Technique

The rapid 4-step technique (RFST) for performing cricothyroidotomy was first described by Brofeldt and others as an attempt to simplify the procedure. The first of the four steps is similar to the first step of the standard technique, except that the surgeon performs the procedure from above the head of bed. Incision is then performed with a horizontal stab through skin, subcutaneous tissues, and CT membrane simultaneously, gaining access to the airway. Stabilization of the larynx is next achieved via insertion of the hook against the cricoid cartilage, before placement of the tracheostomy tube as previously mentioned.

This method was considered simpler since it required fewer steps and instruments, and it replicated physician positioning for orotracheal intubation. Randomized crossover trials compared the time required to achieve a surgical airway and complication rate between the two surgical techniques. The RFST was performed in about one-third the time required to perform the standard technique. However, the RFST was associated with a higher rate of complication, mainly cricoid fractures, in cadaveric models.

Percutaneous Cricothyroidotomy

Percutaneous cricothyroidotomy is considered by many non-surgeon operators to be simpler to perform than standard surgical technique. It involves less surgical dissection and can be learned easily by anesthesiologists, emergency physicians, or intensivists due to similarities with central venous catheter insertion techniques. However, the technique still mandates strict knowledge of the anatomy and CT membrane localization. It also includes multiple steps, approaching the open surgical technique in complexity. At present, there are multiple commercially available prepackaged kits for percutaneous cricothyroidotomy (Melker Emergency Cricothyroidotomy Catheter Set, Portex Mini-Trach II, Pertrach, etc.), most of which are based on the Seldinger technique.

A small vertical skin incision is made over the CT membrane after identifying the landmarks and fixing the larynx in place with the nondominant hand. Then, an 18-gauge needle attached to a syringe is introduced through the CT membrane, and proper positioning is confirmed with aspiration of air. A guide wire is then inserted through the needle into the airway after the syringe has been removed. The needle is removed with care taken not to pull out the guide wire, and a cannula on a dilator is introduced into the airway over the guide wire. After the cannula is sitting completely against the anterior neck, the dilator and guide wire are removed.

Unfortunately, contradicting reports in the literature depict no clear evidence as to which cricothyroidotomy technique is the best in an emergency situation. Studies comparing the wire-guided Seldinger-based technique to the standard surgical technique in human cadaveric models showed a success rate up to 93% with the Seldinger technique compared to 84–86% with the surgical technique. In a recent study by Schober and others, though, the percutaneous wire-guided technique was associated with more complications than the surgical technique, required a longer insertion time, and had a lower success rate (71% vs. 100%). The discrepancy in findings may be explained by differences regarding qualifications of the study participants. Emergency physicians are generally more experienced in using wire-guided techniques for central venous and arterial catheterization, while medical students, whose data was presented in this latter study, have very little experience in the technique.

Postoperative Considerations

As cricothyroidotomy is frequently performed under emergent conditions for upper airway obstruction, after surgical access is stabilized, the airway should be examined either by flexible endoscopy or formal bronchoscopy. If there is an obvious reversible process that caused the airway obstruction, proper action should be undertaken, e.g., foreign body removal. Postoperative chest x-ray is important to rule out pneumothorax or pneumomediastinum. Standard tracheostomy tube hygiene should be quickly initiated: humidification, frequent cleaning of an inner cannula, suctioning, monitoring of cuff pressure to avoid unnecessary mucosal injury, and vigilant skin care.

Though some authors advocate long-term use of a cricothyroidotomy site for airway, most advocate formal conversion to tracheostomy, primarily due to concern for subglottic stenosis. The timing of cricothyroidotomy conversion to tracheostomy continues to be controversial in the literature. Jackson advocated an immediate conversion "as soon as the patient has reestablished his breathing." Commonly, if access is needed for longer than 48–72 hours, the cricothyroidotomy will be converted to tracheostomy. Since data supporting routine conversion is lacking in the literature, and several retrospective studies do not suggest clear benefit from cricothyroidotomy conversion, prospective investigation should be designed to settle this issue.

Complications

The reported complication rate for emergent cricothyroidotomy ranges from 10% to 40%, and for elective procedures ranges from 6% to 8%. Even though emergent cricothyroidotomy can be associated with significant morbidity, these potential complications must be compared to the mortality rate for patients with severe airway obstruction who cannot be intubated. The rates of complication for elective cricothyroidotomy are similar to reported complications for elective tracheostomy. Early complications include failure to establish an effective airway, hemorrhage, aspiration, pneumothorax, pneumomediastinum, esophageal perforation, vocal fold injury, and laryngeal disruption.

There are multiple scenarios in which cricothyroidotomy fails to establish an airway. Either a delay in initiation of the procedure or prolonged operative time can lead to extended hypoxia, brain damage, and death. Also, the tracheostomy or endotracheal tube may be placed unsuccessfully, leading to creation of a false tract within the neck. The most frequently cited complication by McGill and others in 1982 was incorrect placement of the tube through the thyrohyoid membrane. Proper identification of landmarks during the procedure and a vertical skin incision help prevent this complication.

Severe bleeding either during or immediately after cricothyroidotomy is rare. Hemorrhage is most commonly due to injury to a superficial vein, which the vertical midline skin incision also avoids. A horizontal incision through the CT membrane should avoid branches from the CT artery. During needle or percutaneous cricothyroidotomy, decreased airway protection can lead to aspiration of secretions, emesis, or blood, leading to possible pneumonia or hypoxia.

Long-term complications of cricothyroidotomy include laryngotracheal stenosis, aspiration, dysphagia, dysphonia, tracheoesophageal fistula, infection, delayed hemorrhage, laryngo-cutaneous fistula, tracheomalacia, and tube obstruction. Dysphonia is a common complication, in some reports occurring in 50% of cricothyroidotomy patients. Patients report hoarseness, weak voice, or decreased pitch range, which may be related to injury to the superior laryngeal nerve or cricothyroid muscle, or scarring of the anterior thyroid and cricoid cartilages.

Laryngotracheal stenosis can be a difficult complication, requiring multiple surgeries and possible chronic tracheostomy dependence. In a large literature review focused on complications following cricothyroidotomy, Burkey and others identified four groups of patients at increased risk for subglottic stenosis: patients with underlying laryngeal pathology, prolonged endotracheal intubation, airway obstruction after previous intubation, and pediatric patients. Esses and Jafek found that almost 3% of cricothyroidotomy patients will suffer chronic airway obstruction and/or a voice disorder. A recent meta-analysis found a similar 2.2% rate of chronic subglottic stenosis following cricothyroidotomy. Therefore, cricothyroidotomy is frequently successful but should not be considered a benign procedure.

Conclusions

Despite an increasing number of alternative airway rescue devices, the surgical airway remains the final approach on all difficult airway algorithms. Cricothyroidotomy is a relatively straightforward procedure with a high success rate in those with adequate training. In an emergent setting, cricothyroidotomy offers the quickest route to stabilizing the airway and should be the first-line therapy. However, as an elective procedure, cricothyroidotomy is only appropriate in some cases, most notably in those without antecedent intubation or laryngeal pathology.

There are a number of techniques for cannulating the airway through the cricothyroid membrane, including needle cricothyroidotomy, open surgical approach, and percutaneous dilational cricothyroidotomy. Patient age and relevant neck anatomy, operator experience, and available equipment most often determine the appropriate technique. Complications of cricothyroidotomy are relatively rare and compare favorably to those following tracheostomy when performed in carefully selected patients. Postoperative laryngotracheal stenosis, historically thought to be a routine consequence of cricothyroidotomy, only occurs with significant frequency in patients outside of standard inclusion criteria.

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Transtracheal Oxygen Catheter Placement and Management

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Kent L. Christopher

Historical Perspective

Much like any other procedural technology utilizing a specific device, there is a natural process for a series of changes to occur over time in the device design and method of use. Such is the case for transtracheal oxygen therapy (TTO). In 1982, Henry Heimlich first described percutaneous placement of a transtracheal catheter between the second and third tracheal cartilages for supplemental oxygen delivery in 14 patients. TTO was initially administered using a custom device consisting of a 16-gauge Teflon intravenous catheter externally secured by a reversed pediatric tracheostomy tube that was fastened about the neck with cloth ties. Heimlich and Carr described their experience with a larger patient population in 1985. Heimlich eventually designed a commercial product that consisted of a modified 16-gauge Teflon catheter that was inserted through a companion needle (Micro-Trach, Erie Medical, Milwaukee, WI). The final version of the Heimlich device (Micro-Trach, Ballard Medical Products, Draper, UT) was commercially available from 1990 to 1993.

In 1986, Leger and coworkers from Lyon, France, described a TTO catheter that was inserted using a needle-guidewire-dilator, or modified Seldinger technique (MST). A small number of patients with hypoxemia refractory to nasal cannula administration were evaluated, and the larger-diameter catheter delivered higher flows (mean = 2.9 L/min) to achieve adequate oxygen saturations. The catheter and companion introducer system (Oxycath, Laboratorie Smad, Labresle, France) were commercially available in Europe, but not in the United States. One year after Leger and colleagues introduced the Oxycath, Johnson and Cary described an implantation procedure involving subcutaneous tunneling of a silicone TTO catheter from the mid anterior chest to extend approximately 2 cm into the lumen of the trachea. The catheter (ITOC, Cook Critical Care, Bloomington, IN) was commercially available until the year 2000.

Our initial experience in transtracheal oxygen was with the management of patients with severe hypoxemia that was refractory to nasal cannula therapy. We originally developed a TTO catheter system in the mid-1980s that utilized an MST for insertion. We then reported on the safety and efficacy of a comprehensive MST transtracheal oxygen therapy program in 1987 (the Spofford Christopher Oxygen Optimizing Program). The acronym SCOOP Program was later coined. In the mid-1990s, the SCOOP Program was expanded to also accommodate a surgical method for insertion and management strategy for transtracheal oxygen therapy. The SCOOP Program continues to be the most widely used method of TTO administration worldwide, and the only products that are commercially available at the present time relate to this method of TTO administration. The majority of the research and clinical experience are based upon this technology. Consequently, the remainder of this chapter will focus on the SCOOP Program for transtracheal oxygen therapy. Both the MST and the surgical technique will be presented. The potential benefits of TTO therapy, complications, patient selection, transtracheal procedures, patient management, and catheter care are discussed.

Potential Benefits

Overview of Prior TTO Study Designs

Subjects serve as their own control in most studies. In short-term physiologic studies, patients with an existing tracheocutaneous fistula usually received interventions related to tracheal gas delivery in a random order, then were compared to control evaluation with no tracheal flow. In the long-term clinical studies, data collected after initiation of TTO therapy were compared to data collected while the patient was receiving LTOT by nasal cannula. One investigation randomized

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Table 68.1 Potential benefits of transtracheal oxygen therapy

Correction of hypoxemia unresponsive (refractory) to nasal oxygen
Reduced hematocrit
Reduced cor pulmonale
Decreased pulmonary vascular resistance
Improved room air A-aDO_2
Reduced inspired minute volume
Decreased tidal volume
Decreased dead space volume
Improved or maintained $PaCO_2$
Decreased work of breathing
Decreased T_i/T_{tot}
Improved exercise capacity
Reduced dyspnea
Reduced flow requirements during rest (55%) and exercise (30%)
Improved activity
Improved comfort and cosmesis
Improved physical, psychological, and social function
Improved duration of oxygen use (compliance)
Reduced days of hospitalization

A-aDO_2 alveolar-to-arterial oxygen tension gradient, *$PaCO_2$* arterial partial pressure of carbon dioxide, *T_i/T_{tot}* time of inspiration relative to time of inspiration and expiration (respiratory duty cycle)

43 patients to receive LTOT by either TTO or nasal cannula control for the duration of the study. Assessment of complications, contraindications, precautions, and general outcomes is based upon longitudinal studies and clinical experience. These investigations will be reviewed.

Potential Benefits of Transtracheal Oxygen Therapy

The following potential benefits of TTO compared to nasal oxygen delivery are summarized in Table 68.1. A number of physiologic benefits have been described in the literature. Christopher et al. reported a marked reduction in erythrocytosis and cor pulmonale with successful treatment of hypoxemia that was unresponsive (refractory) to maximal flows of standard nasal oxygen therapy. Significant reductions in hematocrit were also seen in patients who were previously thought to be adequately treated with nasal cannula therapy. Oxygen flow requirements were reduced by 55% with rest and 30% during exercise. Domingo and associates reported reduced pulmonary vascular resistance in patients requiring LTOT. Optimal oxygenation was demonstrated during sleep.

O'Donohue evaluated room air arterial blood gases in patients that received nasal oxygen therapy during a control period, and room air arterial blood gases were repeated following administration of TTO. The room air alveolar-to-arterial oxygen tension gradient was significantly less after receiving transtracheal oxygen delivery. In addition, Hoffman and Bloom demonstrated that exercise capacity was significantly increased with TTO. Couser and Make showed that TTO decreases the inspired minute ventilation as a result of a reduction in tidal volume, and Bergofsky and Hurewitz documented reduced physiologic dead space with transtracheal gas delivery. In addition, $PaCO_2$ was maintained or reduced over time. Benditt and Celli reported reduced oxygen cost of breathing and shortened respiratory duty cycle with TTO. Prior studies have demonstrated that a number of potential physiologic benefits of transtracheal gas delivery are directly related to air and/or oxygen flows in ranges up to 6–8 L/min. These potential benefits can be achieved within standard transtracheal oxygen flow rates.

Greater activity may also result from improved physical, psychological, and social function. Oxygen flow requirements with TTO are reduced by 55% at rest and approximately 30% during exercise. Consequently, portable oxygen delivery systems last longer, and patients can take advantage of smaller and lighter units. Activity may also be facilitated by improved exercise tolerance. Some patients have reported reduced dyspnea. Improvement in exercise capacity and dyspnea may result from the previously described reduced physiologic dead space, decreased inspired minute ventilatory requirements, and reduced oxygen cost of breathing.

True 24-h per day compliance can be achieved with TTO therapy. Most patients conclude that TTO is more comfortable than the nasal cannula. Consequently, they are more likely to use TTO continuously. The most common reason for patients to seek TTO was the need for improved comfort. Patients on nasal oxygen may have suboptimal compliance due to discomfort from chronic irritation around the nose and ears or from more significant complications such as contact dermatitis, chondritis, or skin ulceration. Though cosmesis is not a significant concern for many patients, some individuals may be more compliant with TTO due to improved self-image because the delivery device is entirely off the face and can easily be hidden from view.

Cost containment has become an increasing concern. Prolonged hospitalizations are much more costly than long-term oxygen therapy in the home. Compared to a nasal cannula control period, Hoffman showed that hospital days were significantly reduced with TTO. Bloom also demonstrated that hospital days for patients on TTO were significantly less than the hospital days during a period when they had received nasal oxygen. Likewise, the TTO group's hospital days were lower than seen in a separate nasal cannula control population. The prospective randomized controlled study by Bloom also demonstrated improved physical, psychological, and social function with TTO.

Overview of the Program

The SCOOP Program is composed of four clinically defined phases of care:

Phase I: Patient Orientation, Evaluation, Selection, and Procedure Preparation
Phase II: Creation of The Tracheocutaneous fistula
Phase III: Transtracheal Oxygen with an Immature Tract
Phase IV: Transtracheal Oxygen with a Mature Tract

A specific goal in phase I is to define specific benefits that may be of value to the potential candidate. The potential benefits have been discussed. An additional important goal is to exclude individuals for whom TTO is contraindicated. The third task is to appropriately prepare the patient for the procedure while minimizing risk of complications.

The major goals of phase II are to create a quality tracheocutaneous tract and maintain stabilization of the patient. Phase III is focused on a smooth transition to a fully healed, mature tracheocutaneous fistula. The goal in phase IV is to ensure proficiency in catheter and tract self-care with ongoing collaborative care with the physician. The individual phases are the subject of greater discussion in this chapter.

A care team including the interventional pulmonologist as the team leader as well as trained respiratory therapists and nurses administers the TTO program. The surgeon is a key member of the team when the surgical method of tract creation is selected.

Overview of the Two Insertion Techniques

Both the MST and surgical technique developed by otolaryngologist Alan Lipkin, MD (Lipkin procedure) utilize the four phases of the SCOOP Program. Publications for further information regarding both insertion procedures and companion program modifications can be found in the "Suggested Reading" section. Phases I and IV are nearly identical for the two methods, but phases II and III differ based upon the requirements of the methods of creation of the tracheocutaneous fistula.

Though the short-term procedure-specific stents utilized in phase II differ in design, the long-term transtracheal oxygen catheter used in both phases III and IV is identical for both insertion techniques. Complications encountered with the two procedures will be presented. For the variety of reasons identified in this chapter, the author concludes that the Lipkin surgical approach is the method of choice.

Complications with the MST Procedure

The Kampelmacher study is representative of the complications encountered with MST. Results of this large series are illustrated in Table 68.2. An initial experience with 10 patients was compared to subsequent care with the next 65 subjects. Complications were minor. There was a substantial overall reduction in percent complications as the investigators gained experience. Subcutaneous emphysema (3%) was the only complication during the procedure and stent week (phase II). In general, during the immature and mature tract periods (phases III and IV), complications were reduced in frequency of occurrence with experience. However, assuming no patient had more than one event, the prevalence of complications was 34%. The most prevalent complications were keloids (11%), chondritis (3%), inadvertent dislodgement of the catheter with successful reinsertion by clinical staff (9%), and lost tracts that were not recovered (2%). In the 64 patients, they accounted for a complication incidence of 25% and comprised 74% of the total complications. In another two series, catheter dislodgement occurred more frequently at 38% and 44%, respectively. These issues were likely precipitated by inflammation of exposed cartilage during the MST procedure.

A minor complication not identified in the Kampelmacher study was the formation of symptomatic mucus balls, which are accumulations of inspissated mucus on the outer aspect of the catheter tip. They generally occur during the 6–8 weeks when the tract is immature (phase III) during which time the patient cannot routinely remove the catheter for cleaning. Mucus balls cause cough and dyspnea, which resolve when the mucus is removed by the clinician. Reported incidence in three series was 14%, 25%, and 38%. As with any technology, outcomes can vary substantially among caregivers. A variety of factors such as team experience, modifications in the program of care, and the characteristics of the patients selected can all play a role.

Fatalities with the MST have been reported over the past 24 years. There have been rare case reports of one death and five life-threatening events due to airway obstruction from mucus balls. In addition, there has been one case report of death due to tracheal perforation and one report of death due to catheter misplacement.

Complications with the Lipkin Procedure

The surgical technique was initially designed for tract revision in the occasional patient with chronic problems encountered with the MST such as lost tracts, keloids, chondritis, and mucus balls. Kampelmacher utilized the Lipkin procedure to manage another set of 12 individuals from a patient base of an unspecified size with chronic tract problems related to the MST. These included major keloids (6), unrecovered tract closure (3), excessively prolonged tract maturation (1), tracheal chrondritis (1), and mispositioned supracricoidal tract (1). In addition, Kampelmacher selected the Lipkin surgical approach as the initial procedure in two patients with difficult anatomy due to obese neck and one

Table 68.2 Complications of transtracheal oxygen therapy with the modified Seldinger technique

	Initial experience		Subsequent experience	
	Patients (n = 10)	Frequency (%)	Patients (n = 65)	Frequency (%)
Complication				
Procedure and stent week (phase II)				
Subcutaneous emphysema	–	–	2	3
Immature (phase III) and mature (phase IV) tract periods				
Lost tracts	6	60	1	2
Cricothyroid puncture	–	–	1	2
Cephalad-displaced catheter	7	70	–	–
Bacterial cellulitis	1	10	–	–
Keloid	4	40	8	11
Chondritis	3	30	2	3
Inadvertent dislodgement	5	50	7	9
Fractured catheter	1	10	–	–
Tracheobronchitis	–	–	1	2
Tracheitis	–	–	1	2

Data adapted from Kampelmacher MJ, Deenstra M, van Kesteren RG et al. Transtracheal oxygen therapy: an effective and safe alternative to nasal oxygen administration. *Eur Respir J.* 1997;10:828–833

individual with an ossified trachea. Of the 15, one patient had postoperative bleeding. Three had minor keloids excised, and all were doing well at 9 months follow-up.

Lipkin reported complications encountered in 33 consecutive patients who underwent the surgical technique as the initial procedure as compared to 64 consecutive individuals managed using the MST that were followed for a similar period. Chondritis occurred in 12% relative to 25% in MST cohort, and the incidence of symptomatic mucus balls was 15% compared to 44%, respectively. Of note, keloids, temporarily dislodged catheters, and lost tracts were not encountered, compared to 2%, 41%, and 14% in the MST group. No operative complications were experienced. No life-threatening complications or deaths have been reported in the literature since the procedure's introduction in 1996.

Table 68.3 Indications for transtracheal oxygen therapy

General indications (continuous oxygen use)
Resting PaO_2 ≤55 mmHg or SpO_2 ≤88%
Resting PaO_2 56–59 mmHg with any one of the following
Dependent edema
P pulmonale (electrocardiogram)
Polycythemia (hematocrit <56%)
Specific indications
Need for potential physiologic benefits
Complications of nasal cannula
Suboptimal compliance with nasal cannula
Need for greater mobility
Patient preference
Hypoxemia refractory to maximal nasal cannula delivery
Nocturnal hypoxemia despite nasal cannula therapy
Cor pulmonale or erythrocythemia on nasal cannula

PaO_2 arterial partial pressure of oxygen, *SpO_2* oxygen saturation by pulse oximetry

The Lipkin Procedure and Related Program Phases

Phase I: Patient Orientation, Evaluation, Selection, and Preparation

As noted previously, a primary goal in this phase is to select the right patient. The general and specific indications are illustrated in Table 68.3. These recommendations have evolved through data drawn from scientific publications and extensive day-to-day clinical experience. Patients considering TTO should first meet well-established reimbursement criteria for continuous long-term oxygen therapy. These criteria are identified in Table 68.3. Patients only requiring supplemental oxygen during exercise or sleep do not qualify as TTO is intended for continuous use. TTO is specifically indicated for patients needing any of the physiologic benefits noted in Table 68.1. TTO is also indicated for patients who need improved activity and mobility to maintain health. TTO should be considered for patients experiencing complications or discomfort from nasal prongs that result in suboptimal compliance. Patients often remove the cannula if they experience chronic pain or discomfort over the ears or under the nose resulting from abrasion, maceration, ulceration, chondritis, or contact dermatitis.

Hypoxemia that is refractory to maximal nasal cannula therapy is a specific indication for TTO. In addition to refractory hypoxemia, where patients have inadequate oxygen saturations both day and night, there are individuals on continuous oxygen therapy that selectively experience nocturnal

Table 68.4 Contraindications and precautions for transtracheal oxygen therapy

Contraindications
Uncompensated (acute) respiratory acidosis
Upper airway obstruction
Medically unstable
Pleura herniated over procedure site
Severe anxiety neurosis
Mental incompetence
Physically unable to perform catheter care
Poor compliance with medical therapy
Severe uncorrected coagulopathy
Precautions
Poor mechanical reserve
Hypoxemia refractory to nasal cannula
Compensated (chronic) respiratory acidosis
Difficult anatomic access
Mild-to-moderate anxiety neurosis
Uncontrolled bronchial hyperreactivity
Copious or viscous sputum
Serious cardiac arrhythmia
Bleeding disorder
Risk of delayed healing

hypoxemia on nasal prongs. A more subtle subset of patients on long-term oxygen therapy demonstrate adequate oxygen saturations on spot checks during periodic brief medical examinations but continue to experience cor pulmonale or erythrocytosis on nasal oxygen. These individuals may benefit from TTO as an alternative delivery system. Patient preference is extremely important; TTO should be considered when nasal prongs promote noncompliance due to cosmetic, discomfort, or impaired mobility issues.

Contraindications for TTO have been well established and are noted in Table 68.4. Individuals with severe anxiety neurosis tend to become more anxious when faced with the responsibility of catheter self-care. Patients with generalized poor compliance with medical therapy should not be considered. Those with severe mental incompetence or physical disabilities may not be able to adequately care for the catheter. The presence of a severe upper airway obstruction is also a contraindication. Barotrauma could potentially result since oxygen delivered into the distal trachea at a point below the obstruction may not be able to escape. Finally, the finding on a chest radiograph of herniation of pleura over the planned procedure site constitutes a contraindication because the procedure and subsequent catheter insertion may result in rare complications such as pneumothorax or pneumomediastinum. Patients should be medically stable at the time of the procedure. The procedure should be postponed in the presence of uncompensated (acute) respiratory acidosis until the patient is stabilized.

There are a number of patients that do very well with TTO, but one or more precautions (Table 68.4) are identified during their initial evaluation. It is not uncommon for patients on continuous oxygen therapy to have a poor mechanical reserve, profound hypoxemia, or hypercarbia without acidemia. Care must be taken to have these patients on maximal medical therapy and in stable condition prior to the elective procedure. Individuals with a serious cardiac arrhythmia, bleeding disorder, or anticoagulant therapy must be adequately prepared for the procedure and monitored carefully. In patients with an obese neck or other anatomic abnormalities, the Lipkin surgical approach for tract creation is usually necessary as opposed to the MST option.

Some individuals have an element of bronchial hyperreactivity associated with their chronic obstructive pulmonary disease (COPD). Preprocedure pharmacologic control of airway reactivity is important. The presence of copious or viscous sputum in patients with diseases such as cystic fibrosis and bronchiectasis should not necessarily preclude TTO as a treatment option. However, optimal control of bronchial infection and maintenance of adequate bronchial hygiene are essential in this preprocedure phase and throughout the entire program. Individuals with very copious or viscous sputum and those with uncontrolled bronchial hyperreactivity are particularly prone to encountering difficulty in phase III due to the development of symptomatic mucus balls. Unrelenting cough may also predispose marginally compensated patients to respiratory muscle fatigue. The presence of mild to moderate anxiety is not uncommon in patients struggling with severe chronic lung disease. Aggressive education and reassurance often help these individuals overcome their fears, and they usually do well with TTO. Increased confidence often comes with improved mobility and activity.

Ideal candidates are those with nasal oxygen requirements of 2–3 L/min, good pulmonary reserve, stable medical condition, desire to remain active, good adherence to their medical program, and both willingness and ability to follow the TTO care protocol.

Patients should be fully informed about the potential benefits and risks of TTO therapy and surgical approach before making a commitment to proceed with creation of the catheter tract. In addition to a question and answer session with a knowledgeable health care professional, an ideal orientation includes an opportunity for the candidate to talk or meet with a transtracheal patient. A significant other is encouraged to participate in the process. A targeted history should include not only pulmonary information but details about prior oxygen therapy and compliance with the nasal cannula. The history of surgical procedures and anesthesia tolerance is clearly essential.

The physical examination should include careful inspection of the nose including nostrils, septum, and mucosa. The ears are examined for helical chondritis or irritation and other

problems such as serous otitis media. Observations in the neck should include length, thickness, deviation of the trachea, position of the larynx, and position of anterior neck veins. The neck anatomy is inspected and palpated with the transtracheal procedure in mind.

Arterial blood gases on the nasal cannula are helpful to assess the adequacy of alveolar ventilation and degree of compensation for respiratory acidosis. The PaO_2 and respective liter flow give the patient and physician an estimate of reduced oxygen flow anticipated on transtracheal oxygen. The hematocrit is a simple test, which reflects on the overall adequacy of oxygen therapy. A follow-up hematocrit on transtracheal oxygen demonstrating a shift from a high normal hematocrit to a mid or low normal value is common and suggests better 24-h per day oxygenation. Pre- and postbronchodilator spirometry is helpful to estimate mechanical reserve and airway hyperreactivity. Posteroanterior and lateral chest x-rays are of substantial value in excluding rare individuals with pleura over the anterior neck and identifying unusual variants of anatomy before the transtracheal procedure. Additional laboratory data may be beneficial in individual cases. Special tests may include exercise oximetry, a 1.0 FiO_2 study (to determine the degree of refractoriness to oxygenation), lung volumes, diffusion capacity, coagulation studies (anticoagulant therapy), or an electrocardiogram (arrhythmias). Specific preoperative studies are ordered at the discretion of the surgeon. The phase I oversight is generally performed by the interventional pulmonologist, who communicates with the surgeon, shares data, and refers the patient to the surgeon for a preoperative evaluation.

Patients determined to be good candidates for TTO and the surgical method are scheduled for admission to the outpatient surgery center, though some may require in-hospital procedures. An overnight stay in the hospital is arranged to follow the surgery.

Phase II: The Lipkin Procedure and Postoperative Management

In preoperative holding, it is recommended that cephalexin 500 mg or another antibiotic effective against *Staphylococcus aureus* is given for infection prophylaxis. Patients at risk for bronchospasm should receive nebulized bronchodilator about 30 min before the procedure.

Procedure Site Selection

Selection of the proper procedure site is essential for stabilization of the TTO catheter within the tract. Over the years, the SCOOP Program method of site selection has proven to be very effective (Fig. 68.1). The neck should be extended approximately 10 °, usually with the support of a surgical roll placed under the shoulders, and the head supported with a donut. This position aligns the neck and tract for routine catheter insertion during the cleaning process while the patient is looking in a mirror. Procedure site selection and preparation are accomplished utilizing the procedure tray (T-10 Procedure Tray, Transtracheal Systems, Inc., Denver, CO). The superficial anatomy of the anterior neck is palpated, and special attention is paid to anterior neck veins and position of the trachea. The notch of the thyroid cartilage is marked using a surgical marking pen with a "V," the cricothyroid membrane is marked with a horizontal "-----," and the notch of the manubrium is marked with a gentle "U." The cervical trachea rests between the "-----" and the "U" and creates a vertical axis. The most stable position for the catheter is at the crossing of the security necklace and the trachea. The included bead chain necklace is passed around the neck and adjusted with provided wire cutters to accomplish a proper fit, which usually accommodates two fingers snugly but not be excessively tight with neck hyperextension or heavy cough. The crossing point may be marked using the surgical pen with two dashes laterally over the sternocleidomastoid muscles. In about 85% of patients, the necklace will cross at the first or second tracheal interspace. In about 10%, it will cross lower, and in 5%, it will cross the cricothyroid membrane. In this case, the chain is loosened to permit it to dip to the first tracheal interspace. A tract should not be created through the cricothyroid membrane because it predictably results in hoarseness, difficulty with catheter insertion, keloids, and chondritis.

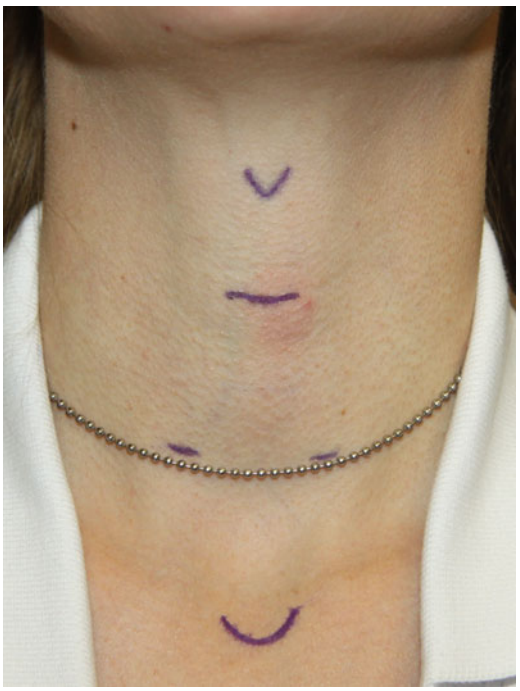

Fig. 68.1 The procedure site is selected

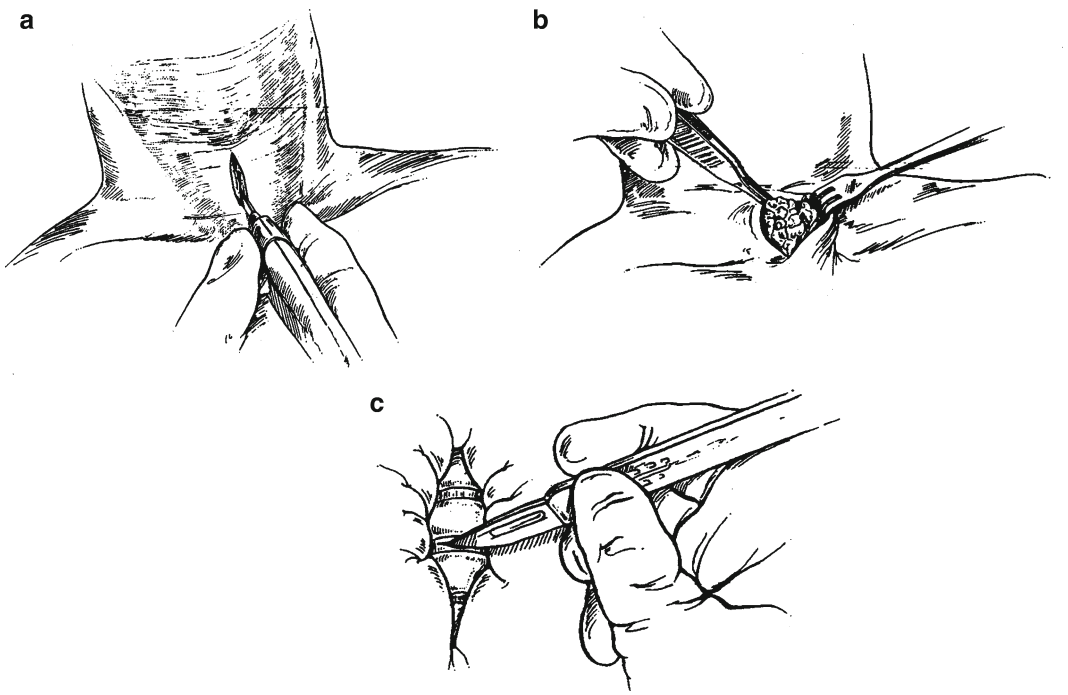

Fig. 68.2 Tracheal access. (**a**) A vertical incision (1.5–2 cm) is made, centered on selected site. (**b**) A cervical lipectomy is performed. (**c**) With the anterior wall of the trachea exposed, skin flaps are sutured to the undersides of the sternothyroid muscles. A small horizontal incision is made in the interspace between the two upper tracheal rings identified during the procedure site selection process (With permission from Transtracheal Systems, Inc.)

Surgical Procedure

Though the patient is placed supine on the operating table, the head of the table may be slightly elevated for patient comfort. The procedure is performed under local anesthesia and intravenous sedation with continuous monitoring by an anesthesiologist. Nasal oxygen is provided throughout the procedure. Although it is rarely necessary, a patient may be converted to general anesthesia on an emergency basis.

The area between the cricoid and sternal notch is infiltrated with lidocaine 1% with epinephrine 1:100,000. The neck is prepped and draped. Using cutting cautery, a vertical incision of approximately 1.5–2 cm is centered on the selected site (Fig. 68.2a). Flaps of full-thickness skin are elevated laterally 2 cm in each direction. The cutting cautery is then used to perform a cervical lipectomy (Fig. 68.2b), removing all the fat down to the level of the strap muscles. The strap muscles are separated at the midline, exposing the anterior wall of the trachea (Fig. 68.2c). Occasionally, division of the thyroid isthmus is necessary.

The previously elevated skin flaps are then used to fashion an epithelialized tract down to the anterior wall of the trachea. This is performed by suturing the flaps to the undersides of the previously exposed sternothyroid muscles with a running suture of 3-0 Vicryl (polyglactin 910, Ethicon, Somerville, NJ) or similar absorbable material (Fig. 68.2c). It may be reinforced with additional interrupted sutures as necessary. Prior to entering the trachea, the entire surgical field is inspected and complete hemostasis is obtained. Additional local anesthetic (lidocaine 1% without epinephrine) is injected into the tracheal wall and lumen, particularly at the point of entry into the trachea. This will help prevent movement and coughing when the trachea is entered. Since oxygen in high concentration is flowing into the trachea, the electrocautery cutting blade should never be used to enter the trachea.

The trachea is then entered with a small horizontal incision in the interspace between two upper tracheal rings (Fig. 68.2c) previously marked by the necklace. The blunt end of the tracheal punch (Fast Tract, Transtracheal Systems, Inc., Denver, CO) is passed through the incision, the punch is engaged, and a small window of cartilage is resected (Fig. 68.3a). Using the available stylet, the stent (Fast Tract, Transtracheal Systems, Inc., Denver, CO) is inserted into the tracheal window (Fig. 68.3b). A tracheal dressing is placed over the procedure site, and ties or straps are then used to secure the stent in proper position. A tracheal collar is applied to the stent to provide humidity for the patient's comfort. Oxygen is supplied by a nasal cannula and/or mask to achieve an oxygen saturation of >90% via pulse oximetry.

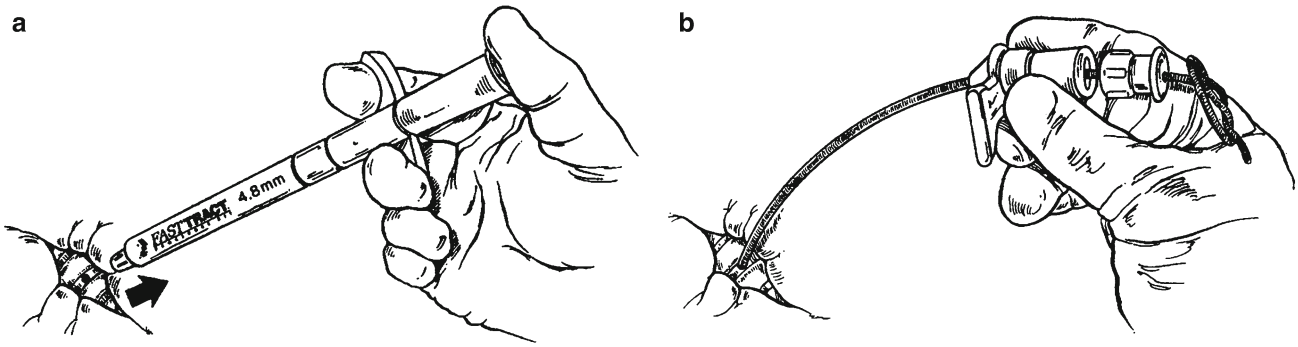

Fig. 68.3 Tracheal window and stent insertion. (**a**) The blunt end of the tracheal punch is passed through the incision, the punch is engaged, and a small window of cartilage is resected. (**b**) The stent is inserted into the tracheal window (With permission from Transtracheal Systems, Inc.)

Postoperative Care

While in post anesthesia recovery or shortly after transfer to the hospital floor, an upright anteroposterior chest radiograph is recommended. This should document the absence of extravasated air (subcutaneous emphysema, pneumomediastinum, and pneumothorax) and confirm the intratracheal location of the radiopaque stent. The relationship of the tip of the stent to the carina is noted. The internal length of the stent is identical to that of the functioning transtracheal catheter with an internal length of 11 cm. If the tip of the stent is closer than 1 cm to the carina, a shorter 9-cm catheter should be obtained before transtracheal oxygen is started the next day. In contrast, if the tip of the catheter is three or more cm above the carina, the 13-cm catheter may be more appropriate.

Antibiotic prophylaxis with cephalexin 250 mg TID (or another antibiotic effective against Staphylococcus aureus) 1–2 weeks following the procedure is recommended. Some exposure of cartilage may be unavoidable. These unusually long periods of prophylaxis appear to be required because of the avascular nature of cartilage and the presence of a foreign body. Substantial clinical experience suggests that failure to administer antibiotic for these longer periods may result in tracheal chondritis 2 or 3 weeks later. As the topical anesthesia wears off during the postprocedure observation time, patients develop some degree of cough. The severity of cough is assessed after the procedure, and an analgesic and cough suppression plan is designed. For individuals with more severe cough, 4 ml of 1/4% lidocaine may be instilled through the stent every hour as needed. Inhaled bronchodilator treatment is recommended for individuals with bronchial hyperreactivity.

Phase III: Transtracheal Oxygen with an Immature Tract

In phase III, TTO is initiated, but the tracheocutaneous tract has not fully healed or matured. A major goal in this phase is to teach the patient proper care in cleaning of the catheter. Other goals in phase III are to prevent inadvertent catheter removal, prevent tract problems, and avoid symptoms from adherence of inspissated mucus to the outer surface of the catheter (mucus balls). To facilitate this, clinicians must periodically evaluate the patient and remove the catheter over a guidewire for cleaning.

Phase III begins the day following the transtracheal procedure. The exchange of the surgical stent for the functioning catheter is either done by the interventional pulmonologist or surgeon. However, as with phase I, the interventional pulmonologist is generally responsible for oversight of phases III and IV. The exchange is accomplished with the patient sitting upright in the bed with a pillow or rolled towel beneath the shoulders. Nasal prongs are rearranged to arrive from behind so as to free anterior neck. The transtracheal catheter is selected based on the position of the stent relative to the carina on the postprocedure radiograph. A catheter with an 11-cm internal length is usually the proper size (SCOOP Program Catheter, Transtracheal Systems, Inc., Denver, CO). A small amount of sterile water-soluble jelly is placed on the tip of the catheter. The customized necklace saved from the initial procedure is passed through the eyelets of the catheter. The atraumatic end of the saved guidewire is passed through the stent up to the black reference mark to clear dried secretions. Approximately 2 cc of 1% plain lidocaine is drawn into a Luer taper syringe and then quickly injected through the stent. The crusts about the stent are cleaned with cotton-tipped applicators dipped in 3% hydrogen peroxide. The ties or straps used to secure the stent in position are removed. The SCOOP Program guidewire is inserted to the black reference mark, and the stent is withdrawn (Fig. 68.4). An assistant holds the black reference mark at the level of the skin to prevent inadvertent removal of the wire. The SCOOP Program Catheter with the prethreaded necklace is then passed over the guidewire and twirled 360 ° into the tract (Fig. 68.5). When the flange comes to rest against the skin, the guidewire is removed and the necklace clasp connected. Placing a 2-in.

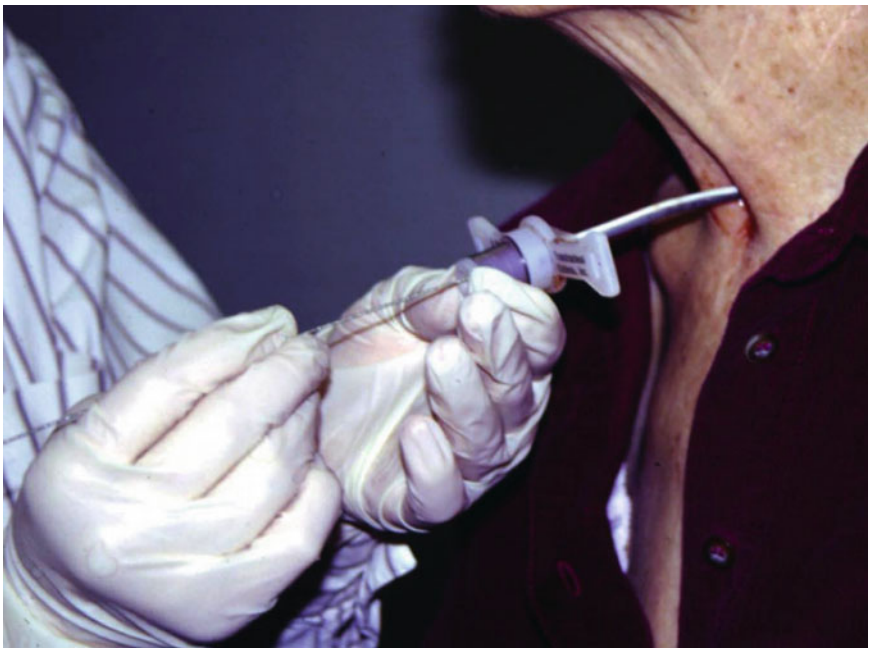

Fig. 68.4 The day following the procedure, the surgical stent is removed over the guidewire

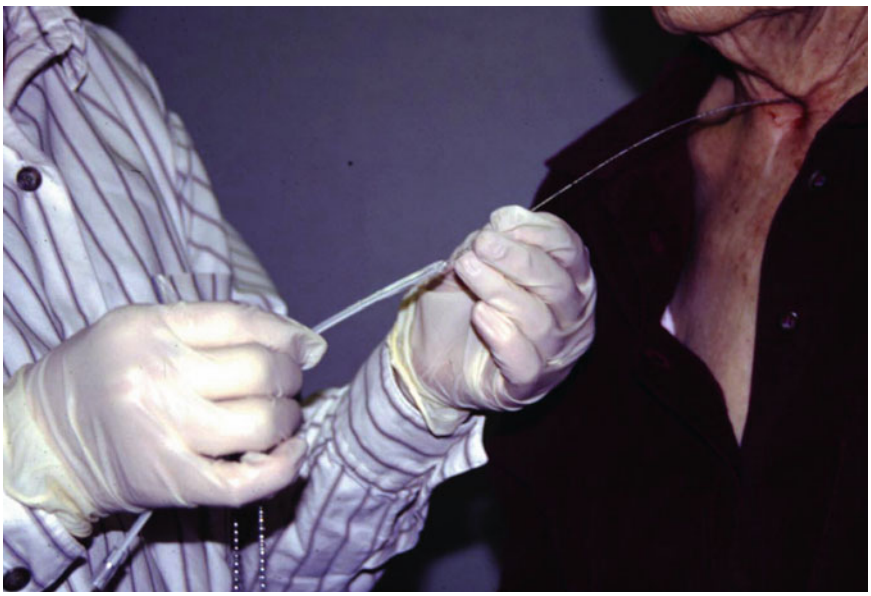

Fig. 68.5 The transtracheal catheter is advanced over the guidewire and into the trachea

piece of clear plastic tape over the necklace immediately right and left of the flange is a simple and effective way to help prevent early dislodgements.

The patient is fitted with a SCOOP Program oxygen hose, and catheter cleaning supplies are dispensed. Pulse oximetry is used to titrate transtracheal flow rates at rest and with exertion. The patient is instructed in cleaning the catheter in place using instilled saline and a cleaning rod. The individual should also be observed through a cleaning cycle to confirm proper technique. Cleaning is recommended two to three times per day. The significant other should be encouraged to sit through the entire session. The patient is educated about security routines to avoid losing the tract and symptoms that suggest the presence of a mucus ball.

A mucus ball is an accumulation of inspissated mucus, which adheres to the anterior and lateral surfaces of the catheter, just above the tip. As noted earlier, symptomatic mucus balls occur in approximately 15% of patients who have undergone the Lipkin procedure, and they occur in phase III when the catheter is cleaned in place. They generally disappear in phase IV when daily removal strips the mucus off the catheter, allowing it to be expectorated. In many patients, the trachea adapts, and mucus balls spontaneously diminish in frequency during phase III. Although mucus balls can cause

a "tickle" cough, dyspnea, or wheezing, they rarely result in airway obstruction. The pathogenesis of their formation is related to the volume of dry gas introduced into the lower airway and baseline secretions. Patients with low FEV_1 and weak cough are less able to generate the glottic blast to dislodge mucus balls and are at relatively greater risk. Ineffective cleaning, inadequate humidification, failure to periodically strip the catheter during phase III, and insufficient systemic hydration are iatrogenic factors which predispose a patient to mucus ball formation. The use of a mucoevacuent, such as guaifenesin, may be helpful. Clinicians should maintain a high index of suspicion during phase III. Mucus balls, which may form in spite of adequate cleaning and humidification, should be immediately recognized and treated.

All patients should return for a clinical evaluation and catheter stripping within the first week of initiating TTO. The catheter stripping technique is very similar to the procedure for exchanging the stent for a functioning catheter. In brief, the patient uses nasal prongs, and 1% lidocaine is instilled into the catheter. The atraumatic end of the guidewire is inserted to the 11-cm mark. With the bead chain disconnected, the soiled catheter is removed and cleaned, while the guidewire remains in place with the black reference mark held at the level of the skin. Water-soluble jelly is applied to the tip of the catheter, which is then reinserted over the guidewire. Once the bead chain necklace is attached and secured with tape, the oxygen hose is connected, and transtracheal oxygen is resumed.

Time required for tract maturation, which spans the duration of phase III, can vary but is generally 10–14 days. One to three visits are required on average. The number of visits during this phase is determined by the need for reinforced education and the patient's propensity to develop mucus balls that require stripping.

Phase IV: Transtracheal Oxygen with a Mature Tract

Phase IV is intended to monitor and prevent complications such as chondritis, keloid formation, and lost tracts. Similarly, the phase is designed to facilitate the patient's realization of the benefits of TTO, including the maintenance of an acceptable level of activity and optimal quality of life. Phase IV usually begins about 10–14 days after the Lipkin procedure in patients with slim and medium necks and perhaps a few days more in patients with obese necks or minimal cervical trachea. A customized cleaning protocol for each patient is desirable because it takes into consideration liter flow, mucus production, underlying lung disease, the patient's level of comfort with catheter removal and insertion, and the ability to generate an effective cough. A cleaning routine should include cleaning in place at least twice a day. The frequency may easily be increased or decreased based on the patient's needs.

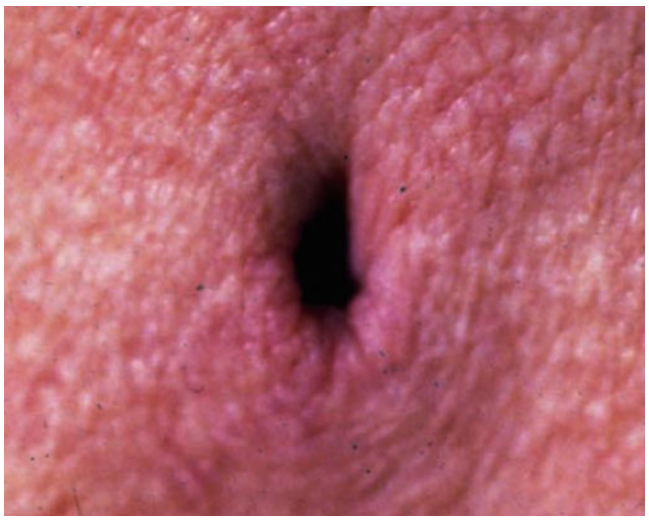

Fig. 68.6 The tracheocutaneous fistula is fully mature

Periodic catheter removal allows for more complete cleaning as well as a reduction in mucus ball formation. It may be performed up to twice daily for patients predisposed to mucus balls. Patients who do not experience mucus balls may prefer to remove the catheter for cleaning less frequently.

A mature tract is fully lined by squamous epithelium. Figure 68.6 illustrates the appearance of a mature tract. When the patient arrives on the first visit of phase IV, tract maturity is assessed. The patient is seated in the procedure chair with a headrest, and oxygen is delivered by nasal cannula. Topical lidocaine is optional during this visit. A new catheter is made ready, threading the patient's necklace through the flange and lubricating the tip with water-soluble jelly. A guidewire is immediately available, but the catheter is removed without inserting the guidewire. If the clinician has difficulty inserting the catheter, the tract is judged immature. The SCOOP Program catheter is reinserted, and cleaning in place is continued for 1 more week. If the physician can easily insert the catheter, the patient is asked to demonstrate the removal for cleaning sequence using a second catheter.

During the remainder of the first visit in phase IV, the patient's necklace fitting is evaluated, the appearance of the tract is noted, pulse oximetry is used to adjust flow rates, and education is emphasized. The security routines, tract care, and cleaning are carefully reviewed.

Patients should not immediately go from cleaning in place in phase III to twice daily removal for cleaning in phase IV. The first week of phase IV is considered a trial period. During the first week, all patients who remove the catheter for cleaning do so only at 8 a.m. Patients who are unable to reinsert the catheter within 5 min should put on nasal prongs and see the physician immediately for help. If the individual needs help, the physician inserts a SCOOP Program catheter with or without the aid of a guidewire. The tract is declared immature, and the patient returns to cleaning in place for 2 more

weeks. Thereafter, virtually all patients are able to progress to catheter removal for cleaning. This trial period concept has dramatically lowered the lost tract rate in phase IV.

Individuals who successfully remove and reinsert the catheter for 1 week may advance up to BID removal for cleaning, as necessary. If needed, this is preferably done at 8 a.m. and 4 p.m. so that any difficulty that may arise would occur during regular working hours when help is more easily obtained. Cleanings in excess of BID should always be done using an in-place method; excessive removal and reinsertion may traumatize the tract and result in tenderness or chondritis.

Chondritis rarely occurs in phase III but may present in phase IV. The prevalence is approximately 12% when the Lipkin procedure is used. Cartilage is a unique tissue because it is avascular and has a tendency to become colonized by bacteria and behave like a foreign body. Refer to the earlier discussion justifying the prolonged use of antibiotic prophylaxis around the time of the procedure. Patients develop a deep indurated lump around the tract which, when present, usually occurs several weeks after the procedure. The lump is often tender, but unlike an abscess, it is not fluctuant. The bacteriology is unclear, but the knot appears to be a regional inflammatory response to colonization of exposed tracheal cartilage. Treatment with oral antibiotics effective against Staphylococcus aureus for an additional 3 weeks is usually effective.

Lost tracts and keloids may appear months or years of TTO but are uncommon following the Lipkin procedure. Small keloids may respond to repeated injection of small amounts of deposteroid (e.g., Kenalog, Depo-Medrol) directly into the keloid. More aggressive excision may be required if keloids obstruct the tract opening during catheter insertion.

A major focus in phase IV is to keep the patient active, mobile, and participating in a collaborative care program for health maintenance. Figure 68.7 shows the transtracheal catheter system in place in a phase IV patient, and Fig. 68.8 illustrates optimal activity on TTO.

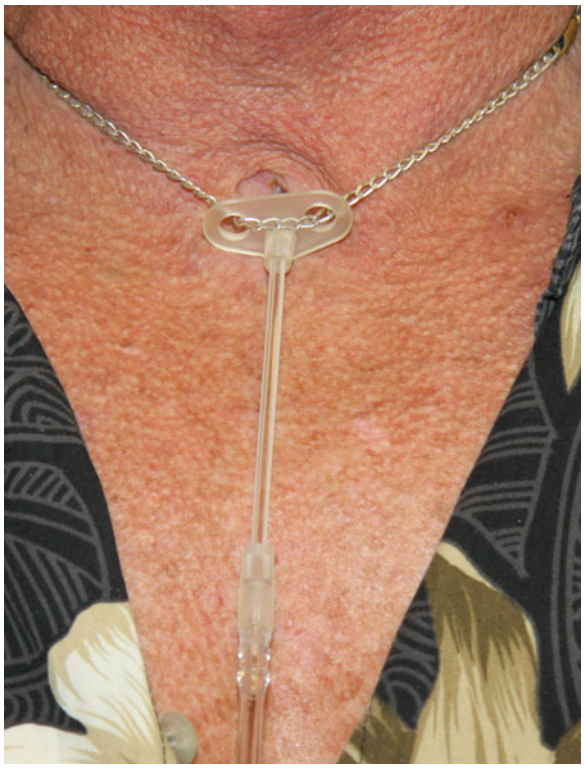

Fig. 68.7 The transtracheal catheter is secured with the necklace and attached to the oxygen supply via the oxygen hose

Fig. 68.8 An active patient enjoys fishing on TTO. The catheter and hose are concealed under upper body clothing, and the lightweight portable oxygen supply is carried in a specially designed backpack

The Modified Seldinger Technique for Catheter Placement and Companion Phases

MST Procedure and Stent Week

The Lipkin procedure and companion program are superior to the MST method for a variety of reasons outlined in the next section of this chapter. However, the MST method will be briefly reviewed for completeness. As with the Lipkin procedure, references for full description and important details of the MST and companion program can be found in the "Suggested Reading" section.

The MST procedure generally takes place on an outpatient basis. Proper patient selection and preparation should occur similar to that which is described in phase I of the Lipkin procedure section. The MST procedure should be performed with the patient sitting upright, and ideal positioning is achieved with an ENT examination chair with a headrest. Procedure site selection and preparation are as previously described. Using the upper tier of the procedure tray (T-9 Procedure Tray, Transtracheal Systems, Inc., Denver, CO), skin anesthesia is performed using a 27-GA needle with 2% lidocaine with epinephrine 1:100,000 at the level where the necklace crosses the cervical trachea. A 20-GA needle is inserted into the trachea at the puncture site, and local anesthetic is quickly injected. A no. 15 scalpel is used to make a vertical 1-cm incision at the selected puncture site, avoiding anterior neck veins. The 7-cm 18-GA thin wall needle attached to a syringe containing 2 ml of sterile saline is passed through the small incision down to the trachea. The cartilages are gently palpated with the needle, which is then popped through the intercartilaginous ligament. Air is aspirated back, and the syringe is detached from the needle. The atraumatic end of the guidewire is inserted through the needle to the 11-cm reference mark. The dilator is passed over the guidewire with a firm and steady push, and twirling the dilator is not necessary.

The dilator is removed taking special care to leave the guidewire in place. This technique is different than insertion of a central venous catheter because of the absence of an introducer sheath. The previously lubricated stent is immediately inserted over the guidewire. As the tip passes through the neck tissues, it is twirled a full 360 ° until the flange comes to rest against the skin. The stent is stabilized with sutures passed vertically through full-thickness skin. As the stent is being sutured in place, the patient is asked to cough gently, and air should vent outward through the stent lumen, confirming position within the airway. The 1-cm vertical incision is not closed with sutures and should be intentionally left open to permit the stent to function as a surgical drain. A nonocclusive dressing is lightly taped over the flange of the stent, and the procedure is terminated.

During postprocedure care, a posteroanterior and lateral chest x-ray is obtained to confirm proper placement of the stent and absence of complications from extravasated air. Patients are observed for a minimum of 1 h following the procedure prior to discharge. Individuals with impaired mechanical reserve, refractory hypoxemia, or chronic hypercarbia may be admitted to an observation unit overnight. The physician should also admit to observation unit other patients who would be a concern at home. The remainder of the postprocedure care is as outlined in the Lipkin procedure section. However, experience with the MST calls for the stent to remain in place for 7 days.

Phases III and IV

The immature tract phase is similar to that of the Lipkin procedure but is more complex and of a longer duration. Healing of the tracheocutaneous fistula to allow for catheter removal for cleaning has a duration of 6–8 weeks. Patients require a greater number of visits for catheter stripping and reinforcement of education. Phase IV is similar to the Lipkin method. However, fewer patients fail the trial period with the Lipkin method, as the tract is less likely to close.

Lipkin Procedure and Program: The Method of Choice

There are compelling reasons for selecting the Lipkin procedure and companion SCOOP Program over the MST method. Compared to the MST, there is a lower incidence of complications, particularly mucus balls, chondritis, lost tracts, and keloids. TTO can be initiated within 24 h, avoiding a 7-day delay. Because of the superior tract formation and more rapid healing, the immature tract phase can be reduced from 6–8 weeks down to 10–14 days. Consequently, return visits for catheter stripping to avoid mucus balls are reduced. Emergent visits for tract recovery are rare. As a result of these benefits, demands on clinician time and resources are minimized. Both clinician training and patient education are simplified. Finally, the shorter, streamlined program facilitates referral center treatment of out-of-town patients.

Reimbursement

The interventional pulmonologist is reimbursed for patient encounters during the program phases for both the Lipkin procedure and MST methods under standard Current Procedural Technology (CPT) evaluation and management codes.

The Lipkin procedure has no dedicated code, but surgeons often use "31610 Tracheostomy, fenestration procedure with skin flaps." Since 31610 is not bundled, some surgeons

also elect to use "15838 Excision, excessive skin and subcutaneous tissue (includes lipectomy); submental fat pad."

The CPT used by the interventional pulmonologist for the MST procedure is "31730 Transtracheal (percutaneous) introduction of needle wire dilator/stent or indwelling tube for oxygen therapy." Additionally, the MST code with a modifier has been utilized by interventional pulmonologists for removal of the stent over a guidewire and insertion of the transtracheal catheter. The coding is 31730 with modifier 58 "Staged or related procedure or service by the same physician during the postoperative period."

There presently is no dedicated code for clinician removal and reinsertion of the catheter during cleaning and tract evaluation. This is a periodic necessity, particularly in phase III when the fistulous tract is not mature. Some have used CPT code "31502 Tracheostomy tube change prior to establishment of fistula tract."

Coding is the responsibility of the physician, and reimbursement is clearly subject to payor policy and regional variations in payment amount. The TTO catheters and supplies are presently bundled under the monthly oxygen reimbursement structure.

Other Applications

As noted in the section on potential benefits, transtracheal gas delivery has a variety of potential physiologic benefits that are directly related to standard TTO flows in ranges up to 6–8 L/min. Administration of higher flows beyond what is necessary to achieve adequate oxygenation has additional potential benefits. Transtracheal delivery of a high flow of heated and humidified oxygen/air mixture has been termed transtracheal augmented ventilation (TTAV). Compared to standard TTO, TTAV further decreases inspired minute volume, shortens respiratory duty cycle, and decreases oxygen cost of breathing. TTAV at 10 L/min has been successfully used over extended periods for nocturnal augmented ventilation in TTO subjects with hypoxemia due to severe chronic lung disease. Improved exercise capacity occurred following a 3-month intervention with nocturnal TTAV. TTAV is also used for spontaneous breathing trials in liberation from prolonged mechanical ventilation. Finally, Brack has shown additional physiologic benefits at 15 L/min compared to 10 L/min delivery. Additional benefits of high flows of 15 L/min, when compared to TTO at 1.5 L/min, include reduced respiratory rate and $PaCO_2$ with reduced end-expiratory lung volume.

Prior studies have evaluated TTO for treatment of obstructive sleep apnea (OSA). Flows of 2–6 L/min have improved sleep indices and improved oxygen saturation. Schneider has utilized the TTAV concept with higher flows to resolve obstruction. Anecdotal experience of the authors has shown effective treatment of OSA with nocturnal TTAV in patients who also require daytime TTO for hypoxemia due to chronic obstructive pulmonary disease.

Conclusion

There are multiple potential benefits of transtracheal oxygen therapy. Two very different techniques for creation of the catheter tract have been developed. However, core to the success of TTO is the patient management program. Within the program are two pathways that are tailored to meet the specific needs of their respective companion insertion methods.

Potential complications of TTO have been identified and are generally minor in nature. Outcomes vary subject to the method of tract creation, patient selection, and experience of the team. Indications and contraindications as well as patient evaluation and selection have been discussed. In addition, preprocedure management to address specific precautions and minimize complications has been outlined. Both the surgical approach and MST for tract creation have been reviewed. Patient management during the immature and mature tract phases has been presented. Specific advantages of the Lipkin procedure over the MST have been summarized. The interventional pulmonologist, as team leader, plays a critical role in TTO. Trained respiratory therapists and nurses facilitate program implementation. A surgical colleague adds value to the team.

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Disclaimer Dr. Christopher licensed patents to Transtracheal Systems, Inc. and may receive financial benefit in the future.

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Part VI

Other Endoscopic and Novel Techniques

Natural Orifice Transluminal Endoscopic Surgery (NOTES)

69

Felix J.F. Herth

Over the last 20 years, there have been major advances in endoscopy, both in techniques and instruments. No longer just a diagnostic tool, it has rather quickly and efficiently become one of the best and safest minimally invasive therapeutic tools to address a wide range of pathology. In gastroenterology, for example, it obviates the need to operate on many patients with a variety of neoplastic lesions such as large polyps, submucosal benign lesions, dysplastic lesions and very early malignant lesions.

The development and evaluation of the concept of natural orifice transluminal endoscopic surgery (NOTES) continues to arouse the interest of the medical scientific community. In 1980, Professor Kurt Semm, a gynaecologist, then performed the world's first laparoscopic appendicectomy at the University of Kiel in Germany. Natural orifice transluminal endoscopic surgery (NOTES) is the latest and arguably most significant innovation in surgery since Phillipe Mouret of France performed the first laparoscopic cholecystectomy using video techniques in 1987. This was the index procedure that revolutionised minimally invasive surgical techniques in general surgery.

Gettman et al. reported in 2002 the first ever transvaginal nephrectomy in a porcine model well before NOTES as an entity was defined. However, it was Kalloo in 2004 who brought NOTES into the spotlight when he performed a transgastric peritoneoscopy in a porcine model, opening the door to major developments in the field of NOTES. From that date on, NOTES has been steadily gathering momentum, while growing interest has ensured a steady progress to its evolution. The surgical and medical communities have joined forces to oversee the progress of NOTES taking it safely from the drawing board to the research animal laboratory and finally to the operating room while keeping in sight the lessons learned from the hasty introduction of laparoscopic cholecystectomy and the pitfalls that hindered the progress of MIS.

Since Kalloo performed his groundbreaking NOTES procedure, many experimental porcine procedures have been described, and more recently some very encouraging highly selective human procedures have been successfully completed with no reported morbidity. Despite the fact that early human reports are encouraging, it is still early and possibly premature to generalise the feasibility of this concept.

Why NOTES?

Endoscopic mucosal resection was the evolutionary step before somebody had the courage to breach the muscular layer of the gastrointestinal tract and venture into the peritoneal cavity intentionally and not accidentally. From that point on, progress has accelerated. The possibilities now seem endless, and the massive expansion in the technology brought about by the advances in laparoscopic surgery and endoscopic procedures has given us a huge selection of instruments and devices. As much as helping progress the NOTES idea into a reality in such a short time, these instruments are likely to further enable intraluminal endoscopy to continue its advance.

Varadarajulu et al. surveyed 100 consecutive patients in a medical clinic undergoing endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography for evaluation of abdominal pain, pancreatitis or suspected choledocholithiasis. They were given details of NOTES and laparoscopic cholecystectomy. An overwhelming majority stated that they would opt for NOTES (78%). No significant differences were found in the demographics of those who stated a preference for NOTES versus laparoscopic cholecystectomy. Younger age, female sex and prior endoscopy were independent predictors for choosing NOTES in multivariate model. Lack of pain and visible scar were the most common reasons for choosing NOTES. An interesting

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Table 69.1 Potential advantages of NOTES

• No scars, less pain, earlier mobility and recovery
• Less physiological and psychological trauma
• Feasible alternative to surgery in co-morbid patients
• More ambulatory procedures
• Less overall cost associated with operative care
• Potential to offer therapy outside the operating room environment

finding that was also observed in other studies was the rapidly decreasing trend of patient preference for NOTES as the complication rate increased: 100% preference for NOTES if complications were less than 3%, 97% if complications were 3%, 12% if complications were 6% and only 6% if complications were 9%.

NOTES should therefore offer comparable outcome results to minimally invasive surgery with some superior advantages (see Table 69.1). In reality, however, what will drive NOTES forward is an endless quest for perfection and challenge. If making scars smaller resulted in so much benefit to the patient's recovery and psychology, imagine the potential gains to patients and the health services from a no-scar surgery. If no-scar surgery is what our patients prefer, then this is what they will get if we could prove NOTES's safety and efficacy.

Also, surgeons' perceptions have been studied. The majority (72%) of the 357 surgeons who responded to a survey would be interested in becoming trained in NOTES. Predictors of surgeons being interested in NOTES included age less than 60 years, minimally invasive surgical subspecialty and flexible endoscopy used in more than 10% of the surgeons' cases. The majority of the surgeons believed that NOTES took greater skill to perform and carried a greater risk of complications than laparoscopy, but it would be associated with less pain and faster recovery. About 56% of the surgeons would not prefer to perform cholecystectomy by NOTES; however, most felt they would switch to NOTES if data suggested improved outcomes compared with laparoscopy.

NOSCAR

The skills needed for the safe practice of NOTES cross two specialities: surgery and gastroenterology. For the successful development of this new technique, close collaboration between the two specialities is mandatory. In 2005, 14 leaders from the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) met in New York City to discuss how to develop NOTES from theory into practice safely and efficiently and addressed the challenges, the limitations and the requirements in a white paper published in Surgical Endoscopy. The main goal was to harmonise research and progress in this field and to avoid the pitfalls which were associated with the overly hasty introduction of laparoscopic procedures for certain indications. Recommendations by the working group Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) highlighted the challenges and limitations in implementing NOTES and set guidelines for future development and progress.

Improving Instruments

The medical device companies are racing to devise solutions for every problem we encounter in NOTES. Building on the large innovations in instruments and technology used in laparoscopic surgery (Figs. 69.1, 69.2, 69.3, and 69.4), the

Fig. 69.1 A pulmo-NOTES prototype with two arms and an additional working channel

Fig. 69.2 A whole NOTES system with the steering unit

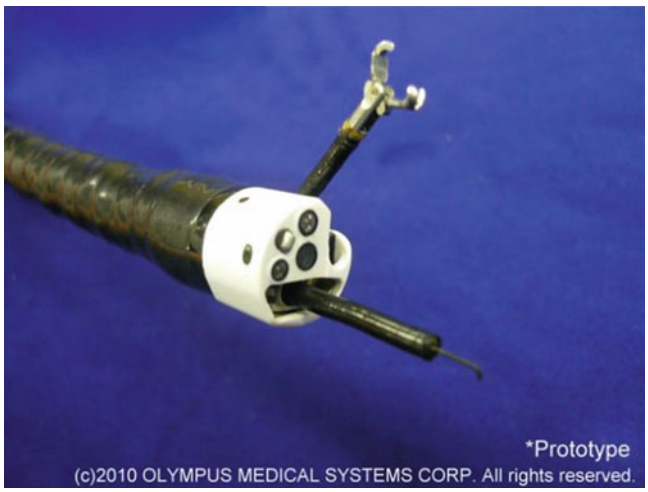

Fig. 69.3 Another NOTES prototype with steerable working channels is shown

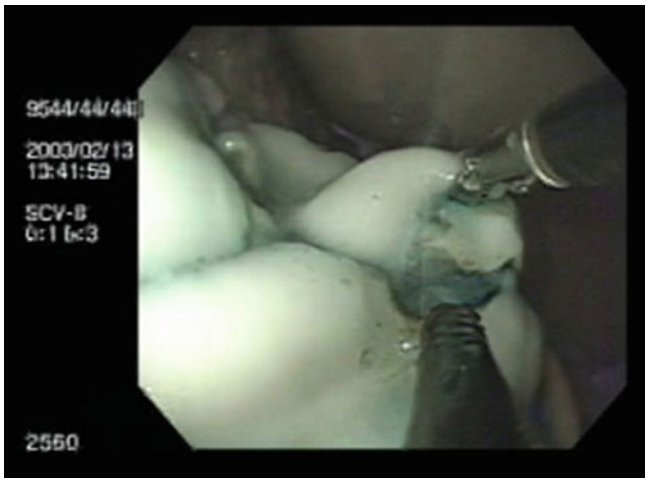

Fig. 69.4 Cutting into tissue with the instrument shown in Fig. 69.3

industry is quickly producing futuristically designed instruments to break down the barriers delaying NOTES's progress. This rush in innovations and design has allowed a steady progress in NOTES over a shorter period of time compared to the early slow progress in the laparoscopic surgery. Enterotomy site closure is currently one of the rate-limiting steps in the race for NOTES transfer from animal models to humans. To achieve an efficient closure, we need a device that allows bimanual tissue manipulation, full-thickness tissue approximation and plication to produce a leak-proof efficient closure of the enterotomy site.

Multiple closure methods and devices have been recently described and are all currently undergoing extensive testing in animal models to determine which one is the most efficient and easy to use. Methods vary from simply using endoclips to more sophisticated instruments with futuristic designs. The target at this stage in NOTES development is to produce a leak-proof closure regardless of the cost. Later on, when different closure methods produce similar results, cost will become an important issue.

Pulmo-NOTES

Thoracoscopy and mediastinoscopy are used as minimally invasive access routes to the mediastinum and pleural cavity and have proven to have clear advantages over traditional open techniques. Such endoscopic approaches allow tissue resection, sampling and staging as well as the application of microsurgical techniques like direct optical magnification of mediastinal pathology. However, the initial enthusiasm and excitement accorded to endoscopic techniques to the thorax have not taken off as fast as may have been first anticipated. The incisions even if small are painful, and the hospital stay is still relatively long, while the complications, although less common, are still significant. Furthermore, they are only applicable to potential targets limited to the outer third of the lung parenchyma.

In contrast, transoesophageal mediastinoscopy and thoracoscopy could eliminate chest wall trauma and allow medial access by using the oesophagus as the entry site into the posterior mediastinum and pleural space. The transoesophageal approach provides a direct ready access to the mediastinum and thoracic cavity allowing a direct visualisation of anatomical structures. The posterior mediastinum in particular is remote from the body surface and delimited by critical and delicate structures, such as the descending thoracic aorta, the oesophagus, the azygos vein and the autonomic ganglia and nerves.

Most diagnostic and therapeutic natural orifice transluminal endoscopic surgery procedures refer to the peritoneal cavity. Only a few experimental studies have addressed natural orifice transluminal endoscopy in other areas of the body such as the mediastinum. Concerns regarding the complications of transoesophageal mediastinoscopy, such as infection and bleeding, secure closure and healing of the oesophageal incision have limited the attempts at such studies. Furthermore, to date, it has not been ascertained whether NOTES mediastinoscopy performed with flexible endoscopes and insufflations of room air increases the risk of cardiorespiratory depression. It has been shown that manual on-demand endoscopic insufflation in the peritoneal cavity occasionally leads to respiratory compromise. Moreover, due to the closeness of critical structures such as the heart and the pleura, mediastinal NOTES might increase the risk of injury of vitally important organs.

It is not surprising that certain pioneers in NOTES are now applying the transoesophageal approach to the thorax. Indeed recently, the technical feasibility and the safety of just

such access have been described in porcine models. It is proposed that such access could greatly enhance the performance of diagnostic manoeuvres such as lymph node resection and pleural biopsy as there is no direct visualisation when these procedures are performed under US guidance (presumably a factor in the relatively high rate of false negative of thoracentesis and blind percutaneous pleural biopsies). Similarly, access to the central region of the chest and to the mediastinum may be facilitated where there is a lesion of this area when compared to a percutaneous approach. NOTES may therefore have the potential to replace mediastinoscopy and thoracoscopy for targeted intervention of medial or hilar lesions.

Oesophageal Access

Because the oesophagus lacks a serosal layer and is a relatively thin organ, leaks may eventually lead to contamination of the mediastinal and/or thoracic cavities. Different techniques for entering the mediastinum are described and tested in animals. The submucosal tunnel technique creates a flap valve that offsets the proximal mucosal incision from the distal incision through the oesophageal muscle layers. With the help of the scope, a submucosal tunnel of 1–5 cm is created using blunt dissection with the tip of closed forceps. A few centimetres proximal to the end of the submucosal tunnel, a needle knife has then to be used to create a small full-thickness incision through the circular and longitudinal muscle layers. Upon withdrawal of the endoscope, the tunnel collapses and can serve as sufficient closure. In a trial by Denise W. Gee, 50% of the tunnels collapsed directly. Additional mucosal clips at the proximal entry site were placed in two swine to further minimise the risk of oesophageal leak and augment the closure.

Other possibilities to close the entry are described by A. Fritscher-Ravens. In her trials, a 2-cm full-thickness oesophageal wall incision was made with a standard needle. The gastroscope was then pushed through the oesophageal wall into the mediastinum.

Oesophageal Closure Techniques

Also for closing the access point in the oesophagus, different techniques are examined in animal models. Secure closure is the fundamental prerequisite for the safe introduction of NOTES. Many of the hybrid case reports used surgical instruments for closure. Most pure NOTES reports used clips with no complications. Most of the technology development has been in improved closure methods.

Endoscopic clips, various T-bars (Figs. 69.5 and 69.6a, b) and suture techniques with two-armed instruments (Fig. 69.7) have been used in pure NOTES experiments. A novel closure technique using autologous mucosal patch has also been described to be feasible in the porcine model.

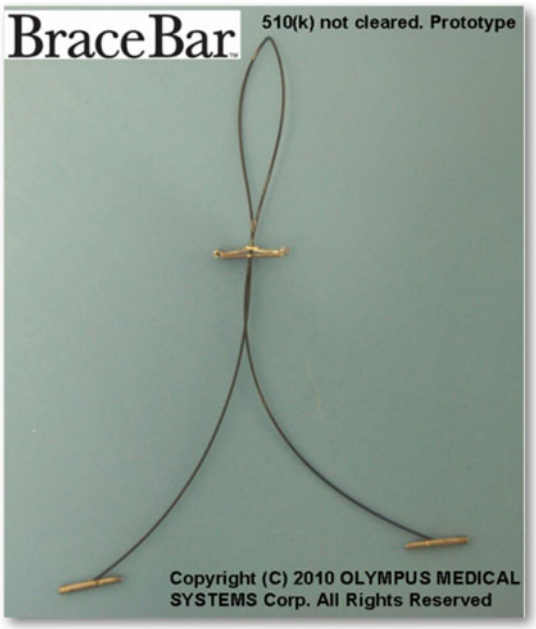

Fig. 69.5 A bar, which can be used to close the incisions

Possible Indications

Tumour Resection

The majority of neurogenic tumours present in the posterior mediastinum. Access to the mediastinum by NOTES may facilitate at least partly conventional operations with these purposes. Abdominal trocar insertion may thereby be at least minimised.

In patients with suspected lung cancer, the presence of mediastinal lymph node metastasis is a critical determinant of therapy and prognosis. Cervical mediastinoscopy is still the current "gold standard" for the assessment of mediastinal lymph nodes. Nevertheless, it allows only limited access to the posterior and anterior mediastinum and aortopulmonary window.

Transoesophageal lymph node mapping and resection could therefore find a role in the provision of complementary and complete staging of the mediastinum in patients with suspected lung cancer as well as in lung cancer patients who require mediastinal tissue staging. The possibility of excising whole nodes is particularly advantageous especially in the case of suspected lymphomas or small-cell lung cancer because of the improved tissue diagnosis in these patients whose primary therapy is most often non-surgical. A NOTES approach could be combined with EUS or EBUS for the precise location and marking of pathologic lymph nodes and

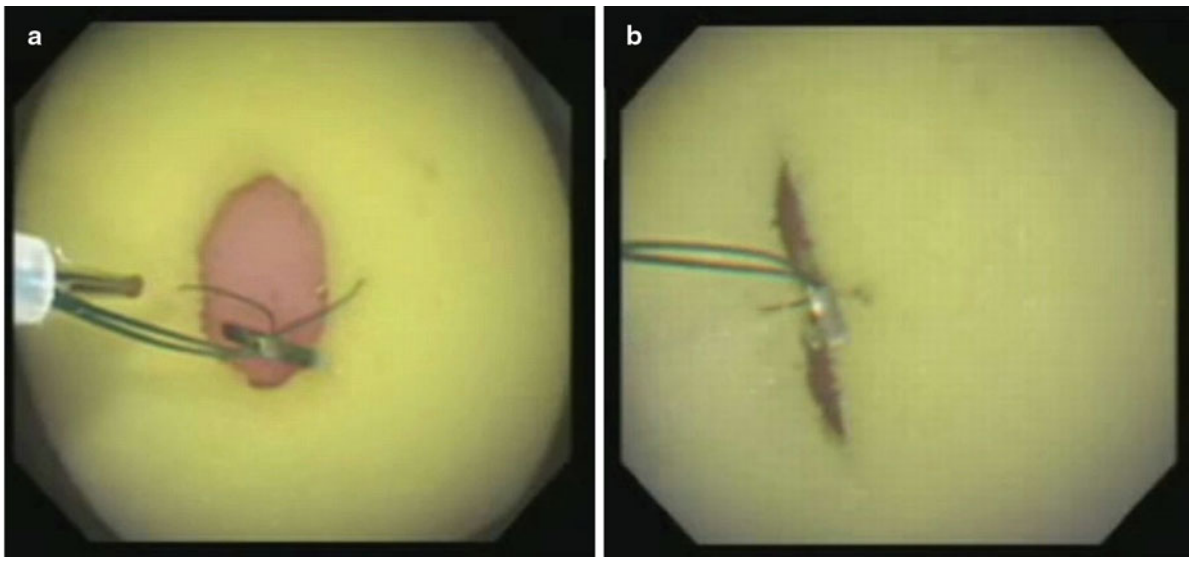

Fig. 69.6 (**a**, **b**) The brace bar in use

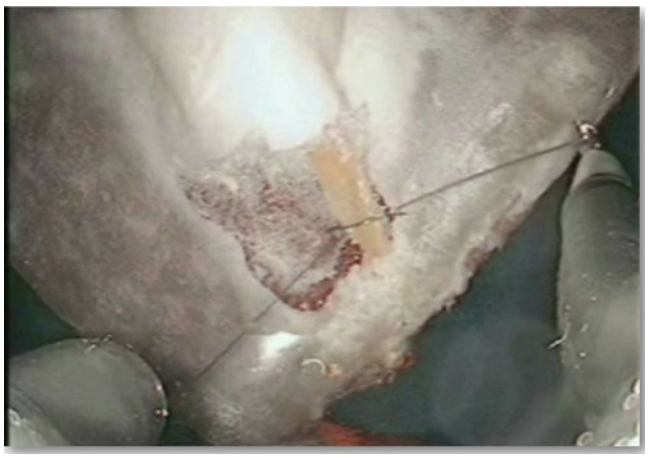

Fig. 69.7 Suturing of an incision with one of the NOTES prototypes

could permit examination and biopsy of lesions not accessible without a minithoracotomy.

Laparoscopic pericardial window creation has been previously described in the management of malignant and recurrent pericardial effusion. Transoesophageal pericardial window creation has also recently been reported in the animal model. It could be performed safely and expeditiously with conventional endoscopic equipment and therefore may have a potential clinical role at the bedside or in the ER setting (Table 69.2).

Disadvantages

Even if the general concept of thoracic NOTES might be appealing, this approach may however pose greater risk for mechanical abrasion and disruption of surrounding structures in comparison to other visceral access routes as well as present a more limited working space due to the constraints of the mediastinum. In addition, the consequences of a leak from the oesophageal enterotomy can be devastating for the patient due to the morbid consequences of mediastinitis. The oesophagus is undoubtedly the most unforgiving organ of the gastrointestinal tract and therefore has been previously considered by surgeons something of a revered zone. The transoesophageal approach in violating the wall of this fragile organ may therefore represent the most aggressive expression of NOTES to date.

Table 69.2 Possible indications for pulmo-NOTES

• Mediastinal cysts
• Mediastinal and hilar lymph node resection
• Tracheobronchomalacia
• Tumour resection

Conclusion

There is still a long way to go before NOTES reaches maturity. It cannot yet be compared to other established surgical approaches. Refinement of indications and the development of instrumentation adapted to the management of access route, retraction, tissue re-approximation and dissection will gradually define its area of application. The publication flow confirmed this trend: few "revolutionary" submissions, but meticulous work in research and development, and much caution in the clinical applications. The development of NOTES is following scientific principles, and this is a good omen for the future.

Suggested Reading

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Percutaneous Endoscopic Gastrostomy (PEG) Tube Placement

70

Maren Schuhmann

Background

The first surgical gastrostomy was described in 1837 and was for a long time the mainstay of direct enteral feeding for patients unable to swallow or feed themselves. It posed significant risks though since patients had to undergo general anaesthesia for this procedure and were often already frail with multiple co-morbidities.

The percutaneous endoscopic gastrostomy (PEG) was first described by Gauderer, a paediatric surgeon, and Ponsky, an endoscopist, and was introduced into clinical practice in 1980. It is a less invasive procedure than a surgically placed gastrostomy, is usually performed under local anaesthesia with only some mild sedation and hence is often more suitable for the patient than a surgical procedure. A PEG provides enteral feeding to patients who have inadequate oral intake for varying reasons but have a normally functioning gastrointestinal tract. Since the first introduction of PEG tubes 30 years ago, they have rapidly gained popularity, and large numbers are performed internationally due to safety and ease of placement.

It is important to remember that enteral feeding access into the stomach or jejunum can also be performed via a radiologically placed gastrostomy or jejunostomy, and this may be suitable for patients unable to undergo oesophagogastroduodenoscopy (OGD) safely.

PEG tubes are generally better tolerated by patients than nasogastric tubes and pose less of a risk at becoming dislodged.

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Indications for PEG Placement

In general, all patients who over a period of 4–6 weeks are unable to maintain an adequate nutritional intake orally due to their underlying disease should receive enteral feeding via a PEG. This includes patients with neurological disorders and severe cachexia due to their underlying disease and also patients who cannot eat or drink safely. Patients with suspected oesophagitis due to radiotherapy for head and neck cancer may require prophylactic placement of a PEG tube.

A PEG may also be placed in cases of malignant bowel obstruction in order to decompress the stomach (so-called venting PEG), for treatment of gastric volvulus and recirculation of bile.

In cases of pyloric stenosis or motility problems of the stomach, a percutaneous endoscopic jejunostomy can be performed.

Whether to place a PEG or not requires careful evaluation of the patient and consideration of the patient and his/her carers' wishes.

Generally, contraindications to PEG placement include a life expectancy of under 4 weeks, incorrectable coagulopathy, acute sepsis, existing peritonitis, perforation of the gastrointestinal tract as well as a technical inability to safely perform an OGD.

Further relative contraindications are the presence of a large volume of ascites, gastric ulcer or gastric malignancy, malabsorption, hepatomegaly, large hiatus hernia, morbid obesity, abdominal wall infection or the presence of large gastric varices.

Preparation

If a coagulopathy is present, this needs to be corrected prior to the procedure. Anticoagulants should be stopped and platelet transfusion given if so required. Some clinicians like

A. Ernst and F.J.F. Herth (eds.), *Principles and Practice of Interventional Pulmonology*,
DOI 10.1007/978-1-4614-4292-9_70,

to perform an abdominal ultrasound prior to PEG insertion to exclude underlying ascites, but this is not routinely recommended.

The patient requires an intravenous access and should be starved for at least 8 h prior to the procedure.

Antibiotic prophylaxis guidelines vary between hospitals, but a standard is often 1.5 g cefuroxime IV prior to the procedure. However, recent studies have shown that antibiotics (co-trimoxazole) given via the PEG tube may be as effective at preventing infections post insertion as intravenous antibiotics.

The patient is usually positioned on his/her back for the procedure, and a mouthguard is inserted. Local anaesthesia is applied to the back of the throat, and many physicians opt for mild sedation with midazolam or propofol. In cases of severe co-morbidities, it may be necessary to perform the procedure without any sedation at all.

Placement of the PEG Tube

Two physicians are required to perform the insertion of a PEG tube, one to operate the gastroscope and the other to perform the puncture in the abdominal wall. Different techniques of insertion are known, such as the most common 'pull technique' (Ponsky) which we describe below. The push technique (Sachs-Vine) is similar except for the PEG tube being pushed over a guide wire. The 'direct introducer' technique (Russell) makes use of the Seldinger technique by directly placing a PEG tube with a balloon at the tip into the lumen of the stomach after dilating the track. Gastroscopy is performed to apply counterpressure whilst inserting the tube and involves the passage of the gastroscope only once.

Complication rates for all these techniques are similar, and only the Russell method may be slightly quicker to perform.

The PEG placement set includes a scalpel, a puncturing needle with stylet, a string, the PEG tube (size 15 or 20 Fr), internal fixation plate and adapter.

Other equipment needed includes the following: syringe, local anaesthesia (1% or 2% lidocaine), sterile gauze, sterile sheets, skin disinfectant, a sterile gown and mask and gloves for the assisting doctor (Fig. 70.1).

It is mandatory that the endoscopist performs a complete OGD and excludes any of the contraindications mentioned above. Wolfsen et al. reported that during initial endoscopy for a scheduled PEG procedure, 36% of the patients had findings such as gastric outlet obstruction or peptic ulcer disease that led to changed management of the patients or abandonment of the procedure altogether. During this time, the assistant cleans the abdomen of the patient with disinfectant (iodine or chlorhexidine) and covers it in a sterile fashion.

The usual point of insertion is the left upper quadrant, a few centimetres left of the midline below the inferior margin of the ribs. The endoscopist identifies a position in the anterior wall of the stomach, usually at the junction of antrum and corpus, for the placement of the PEG tube. The lights in the endoscopy room are then dimmed, and the light at the end of the gastroscope should be visible through the abdominal wall (gastric transillumination). The assistant now pushes his/her finger against the abdominal wall from the outside to confirm the site of puncture endoscopically (Fig. 70.2).

When the correct site is identified, local anaesthetic is infiltrated into the skin and the abdominal wall. At an angle of 90 °, the infiltration needle is advanced further, and the wall of the stomach is punctured taking care not to damage the gastroscope. The needle needs to be advanced until air is aspirated and the needle is visible via the gastroscope in the stomach (Fig. 70.3).

The needle is then removed, and a small incision is made with the scalpel at the site (approx. 5 mm). Now, the puncture needle is advanced, and when inside the stomach, the stylet is removed (Fig. 70.4).

Remember to cover the end of the needle briefly with your finger to avoid air escaping which makes gastroscopy more difficult. After removing the stylet, the double string is passed through the sheath into the stomach. At the same time, the endoscopist passes a forceps through the working channel of the gastroscope and grabs the string (Fig. 70.5).

The forceps are now pulled back slightly into the endoscope, and the entire gastroscope with forceps and grabbed string is removed slowly via the patient's mouth. The string is pulled out of the patient's mouth in order to attach the PEG tube.

The PEG tube is now attached to the string, and the assistant has to pull the string back through the abdominal wall for the tube to pass through mouth, oesophagus and into the stomach until the internal fixating plate is attached to the stomach wall (Fig. 70.6).

The correct positioning of the internal plate is again confirmed via the gastroscope (Fig. 70.7). The top of the tube is cut off, and the external fixation plate and attachments are secured on the tube (Figs. 70.8 and 70.9)

Initially, the external fixation plate is pulled under slight tension and left for 12–24 h at which point it needs to be loosened a little in order to avoid necrosis of the surrounding tissue and to reduce the risk of peristomal infection.

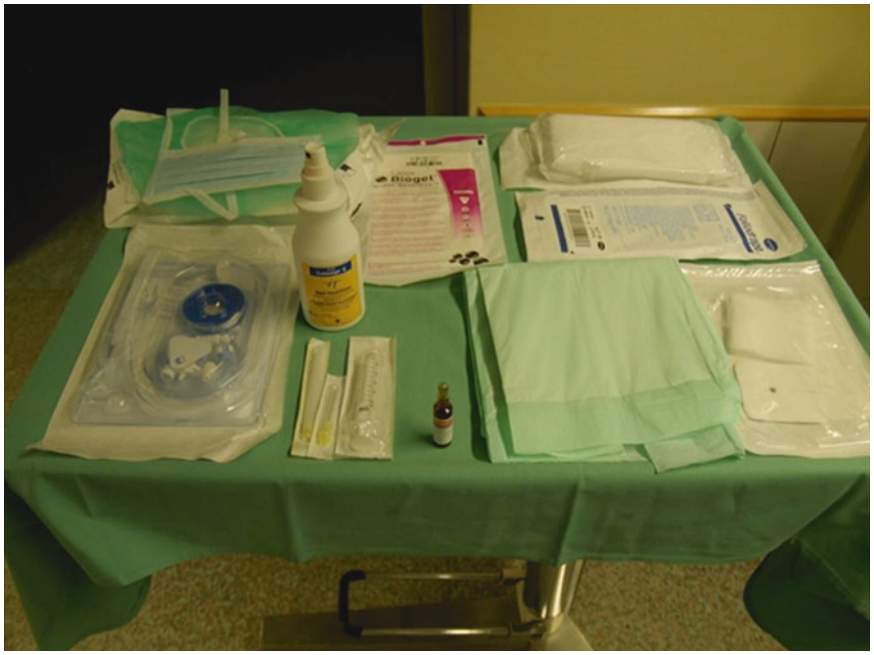

Fig. 70.1 Equipment required for placement of PEG tube

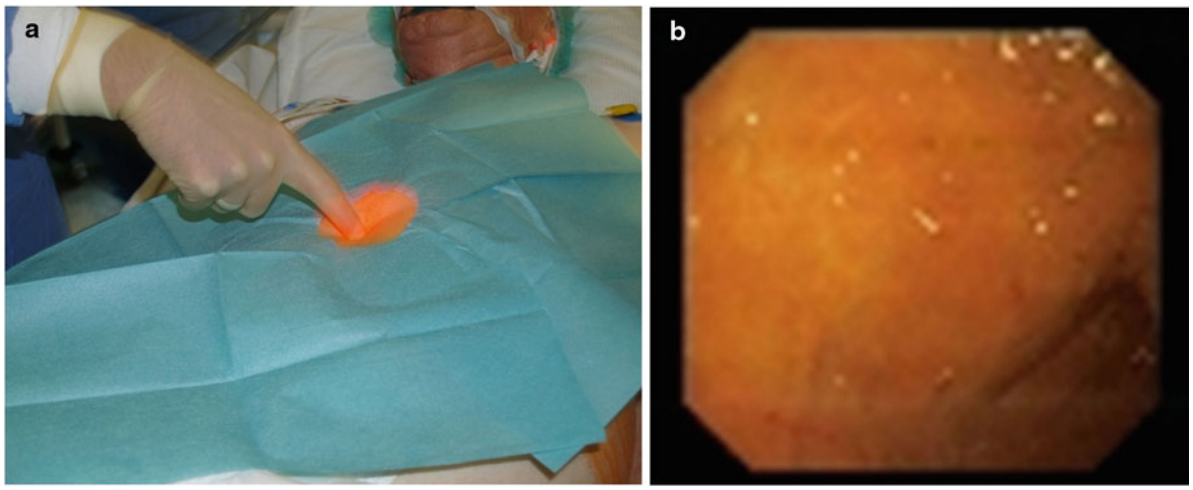

Fig. 70.2 Abdominal transillumination and finger pushing visible endoscopically external (a) and internal (b) view

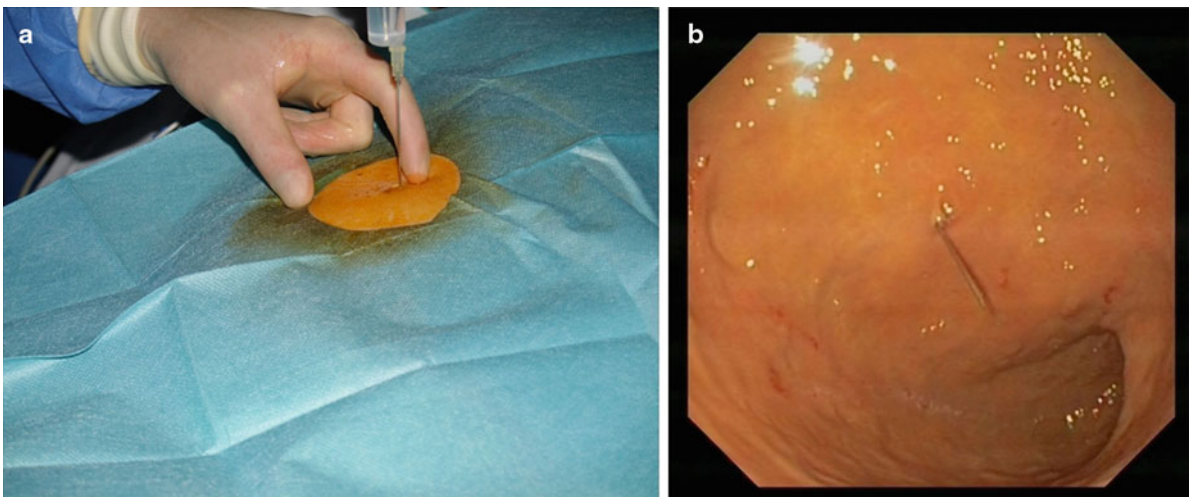

Fig. 70.3 Local anaesthetic infiltration and advancement of needle into stomach, external (a) and internal (b) view

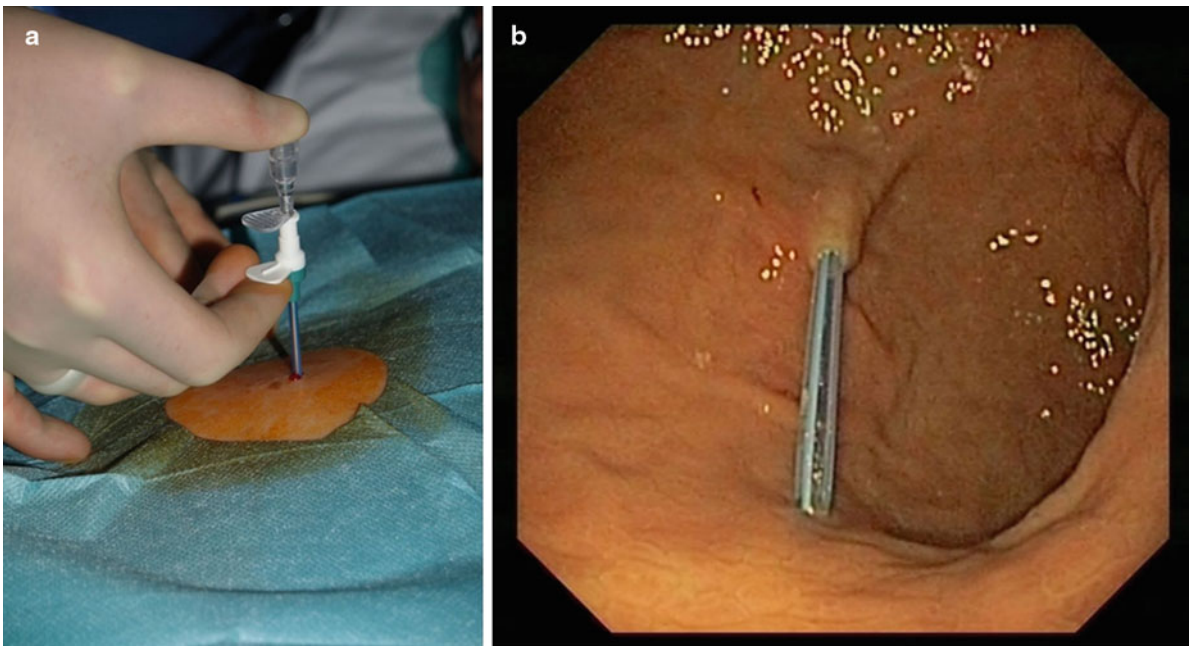

Fig. 70.4 The puncture needle is advanced with stylet, external (a) and internal (b) view

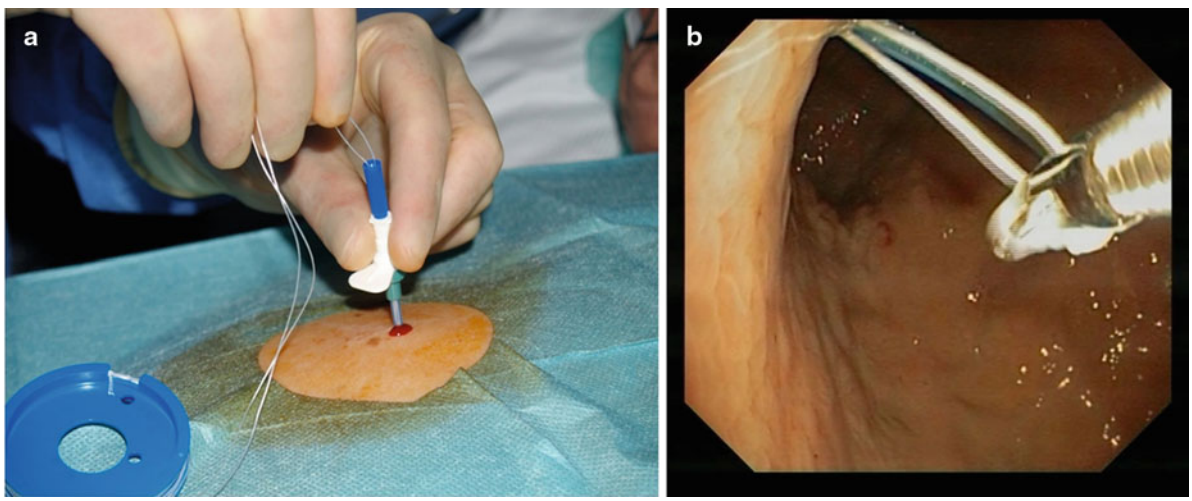

Fig. 70.5 Passing the string through the sheath and grabbing it with biopsy forceps inside the stomach, external (a) and internal (b) view

Complications

The correct selection of appropriate patients for PEG insertion is the single most effective strategy for preventing serious complications. This often requires the involvement of a specialist nutrition team.

PEG tube insertion is associated with a high mortality/morbidity in patients where complications occur, and this needs to be kept in mind when choosing your patients.

During the procedure, complications from oversedation can occur such as respiratory depression, cardiac arrhythmias, aspiration pneumonia as well as cardiovascular problems like hypotension, angina or myocardial infarction.

Haemorrhage at the site of insertion can be seen, but significant bleeding is rare. There may be bleeding in the PEG tract itself, and this can be controlled by tightening the external fixation plate which in turns pulls the internal bumper closer to the stomach wall. Minor oesophageal bleeding

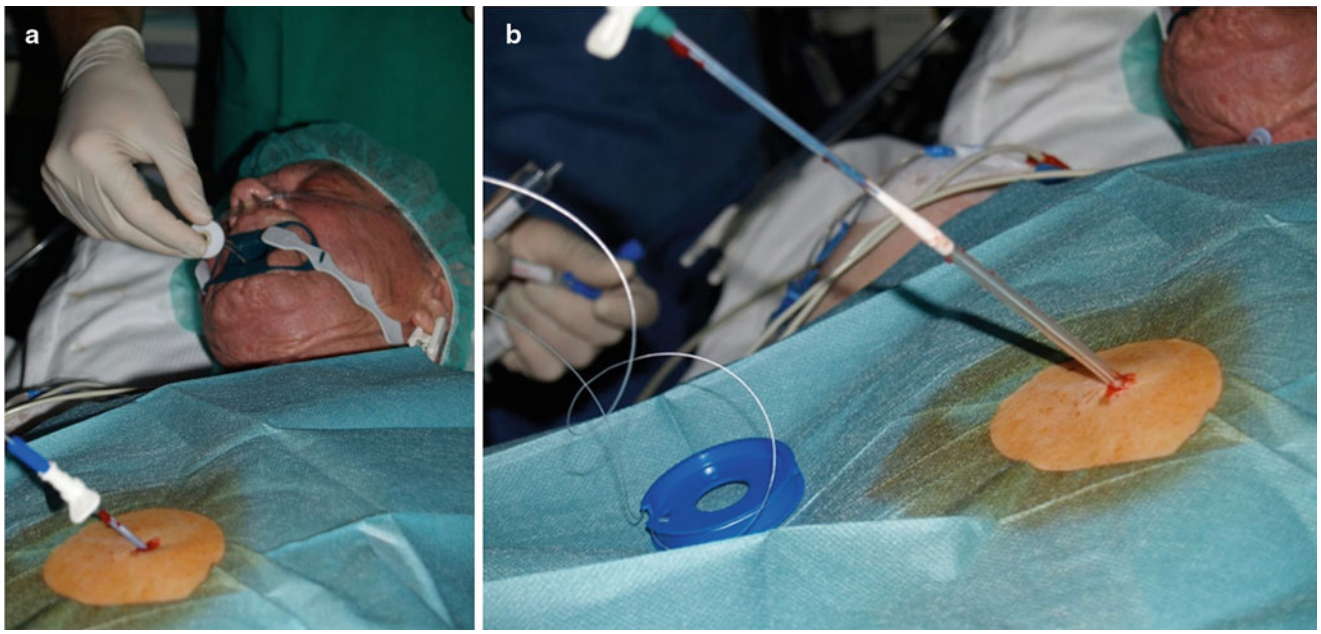

Fig. 70.6 The PEG tube is attached to the string and pulled through the patient's mouth (a) and out of the abdominal wall (b)

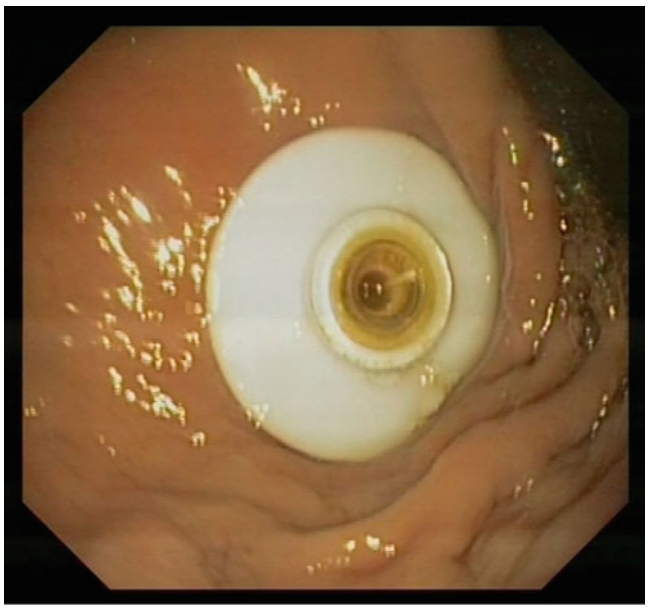

Fig. 70.7 Internal fixation plate visible endoscopically

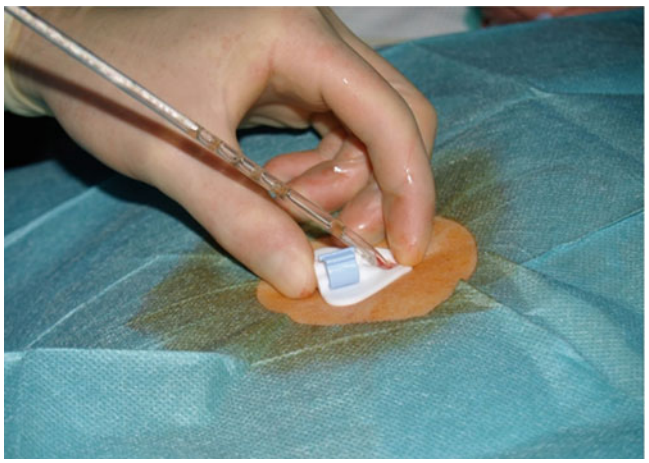

Fig. 70.8 External fixation plate of the PEG tube

can occur when the internal retention disc is pulled through, but more serious bleeding is found if another abdominal structure is accidentally punctured during the procedure. In general, peritonitis is a rare complication (0–1.2%), but any sign of peritonitis after the procedures suggests damage to another viscus such as the small bowel or colon and requires urgent investigation and surgical involvement. Remember that a pneumoperitoneum is often found after the procedure due to the insufflation of air via the gastroscope and the puncture of the stomach lumen. It is therefore not necessarily a sign of peritonitis on abdominal radiograph. A contrast CT scan can be more helpful in these situations when there is a clinical suspicion of having punctured a viscus.

After insertion, mortality remains high due to wound infection, varying between 4% and 30% depending on the extent of the wound infection. The risk of infection is increased in patients with poor nutritional status, advanced age and diabetes mellitus and depends on their underlying disease (more complications occur in patients with malignant disease). In severe cases, an abdominal wall abscess can form, or it can lead to necrotising fasciitis.

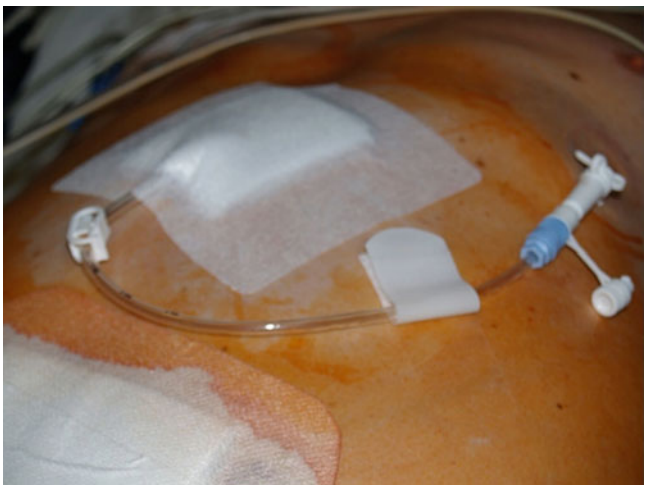

Fig. 70.9 Secured PEG tube with adapter

International guidelines therefore recommend the routine use of a prophylactic antibiotic, given either by intravenous infusion or via the PEG tube once this has been established. The recommended antibiotics are co-amoxiclav or a third-generation cephalosporin.

To avoid peristomal infections, it is advisable to refrain from excessive tightening of the external fixation plate to avoid underlying tissue ischaemia, and it has been suggested to avoid the use of proton pump inhibitors.

Methicillin-resistant *Staphylococcus aureus* has also emerged as a cause for peristomal infections. Some studies have found that nasopharyngeal treatment of known MRSA patients prior to PEG tube insertion as well as a routine antibiotic periprocedure significantly reduced the risk of peristomal infection.

Fungal infections around the stoma site or post insertion can be found but are rare in comparison to bacterial infection.

Later complications include a gastric ulcer at the site of the internal fixation plate or opposite (so-called kissing ulcer), which may lead to significant bleeding. The 'buried bumper syndrome' is another recognised late complication, which can occur if excessive traction is applied to the PEG tube. This is when the internal retention disc embeds within the gastric mucosa and is overgrown by it, resulting in obstruction to the passage of food through the PEG tube. Clinically, it can be detected by an inability to push the PEG tube into the stomach. Endoscopically, it can be seen either as mucosal dimpling, ulceration at the site of the internal bumper or inability to see the fixation plate. A buried bumper may require surgical removal or removal of the granulation tissue with a needle knife papillotome. This complication can be avoided by regularly rotating the tube and by pushing it gently in once a week.

A gastrocolic fistula is a late and rare complication, and it either can be due to tube migration leading to mucosal erosion and fistula formation or may occur when the transverse colon overlies the stomach and is punctured accidentally during PEG insertion. Feed is then delivered into the colon leading to diarrhoea. This is usually only detected when the PEG tube is replaced, and often the patient is asymptomatic. A fistula can be proven by injecting Gastrografin or barium through the PEG, and it requires the removal of the PEG. Usually, the fistula closes within the following week.

It is important to remember that PEG placement does not abolish the risk of aspiration pneumonia in patients who are considered unsafe to swallow. When aspiration occurs, it carries a high mortality rate. It is therefore recommended to let the patient sit upright during feeding periods until 30 min after the feed has gone through to reduce the risk of this complication occurring.

Late displacement will not cause peritonitis, but the track will close within 24 h. It is therefore important either to replace the PEG tube quickly once it has become displaced or to place a Foley catheter through if no PEG tube is available. This will help to maintain the track open.

Tube dysfunction can occur and is defined as peritube leak, fracture of the tube, plugging or tube migration and may necessitate tube replacement. The most common cause is clogging of the tube with medications or enteral formula. It is therefore important to pay special attention that drugs are either dispensed as a liquid or carefully dissolved in water prior to pushing them through the PEG tube. It is also advisable to flush water through the tube after giving any medication to avoid blockage.

Aftercare

Enteral nutrition via the track can begin about 4 h after the procedure. Some physicians prefer to wait for 24 h, but a recent meta-analysis of over 450 patients found no statistically significant increase in complication rates when feeding was started after 4 h.

The gastro-cutaneous fistulous tract becomes established within 2 weeks of PEG placement and may take up to 4 weeks to mature. If the internal retention disc becomes displaced within this period, the tract may break down, and it may require replacement of the tube.

Removal of the PEG Tube

In cases where patients are able to return to oral nutrition or in the case of complications, the PEG can be removed. There are different approaches to PEG removal practised throughout the world of endoscopy. The gastroscope is inserted into

the stomach, and air is insufflated. The PEG tube is pushed into the stomach a short distance, and the internal fixation plate is grabbed with either a two-armed gripping device or a polypectomy loop.

The PEG tube is then cut off above the abdominal wall, and the internal fixation plate can be removed with the gastroscope through the mouth.

Alternatively, some physicians prefer the slightly less invasive procedure of the 'cut and push method' which involves cutting the PEG tube above the abdominal wall and then pushing it through the lumen of the stomach without a simultaneous gastroscopy. The internal bumper plate is then passed through the bowels rather than removing it endoscopically. This has not been shown to have any adverse effects and is cost effective.

Replacement of the PEG Tube

Replacement of the PEG may be required in incidences of tube dysfunction or following certain tube-related complications such as wound infection. Replacement of a PEG tube can be performed endoscopically via the track already created on first placement. This procedure is very similar to that already described, made more simple by the presence of an established track. If it is preferred that the patient is not subjected to multiple future endoscopies or declines this, replacement can be performed with a so-called button. This can be performed with or without the use of a Seldinger wire but is considered to be safer when performed with the wire.

Contraindications to the use of a button are an incompletely formed stoma and a length of the stoma channel of over 4 cm.

The initial button insertion can be performed with or without endoscopy, depending on whether the operator wishes to remove the internal plate orally or whether it is to be left to pass through the bowel. In the endoscopic approach, the patient is prepared as for a gastroscopy, and the gastroscope is inserted into the stomach. The PEG tube is cut off above the abdominal wall, and the soft end of the Seldinger wire is inserted via the PEG stump into the stomach. When the wire is visualised within the stomach, the internal fixation plate is grabbed as described above and removed. Following measurement of the track to calculate the required length of the button, the button itself is then advanced over the guide wire under slight rotation. Once the balloon is seen via the gastroscope in the stomach, it is then filled via the Luer syringe with sterile water, and then the guide wire can be withdrawn.

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Whole-Lung Lavage

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Chakravarthy Reddy

Introduction

Whole-lung lavage (WLL) is a large-volume bronchoalveolar lavage performed primarily for the treatment of pulmonary alveolar proteinosis (PAP). Pulmonary alveolar proteinosis is a primary or an acquired form of macrophage dysfunction that results in abnormal processing of surfactant. Over the course of time, amorphous, acellular phospholipids and surfactant apoproteins accumulate and fill the alveoli leading to impaired gas exchange. This causes a subacute onset of exertional dyspnea which progresses over the course of time. Physical removal of the accumulating amorphous material from the alveoli by a WLL is the most widely accepted and effective therapy for PAP. The procedure involves intubating a patient with a double-lumen endotracheal tube, ventilating a single lung while performing a large-volume (up to 20 L) lavage of the nonventilated lung with the goal of clearing the abnormal proteinaceous material from the alveoli. The details of the procedure are discussed below.

History

The abnormal accumulation of amorphous material in the alveoli of patients affected with PAP was first described in 1958. Initial attempts at treating PAP included systemic antibiotics and corticosteroids and dissolution of the proteinaceous material in the lungs with streptokinase, trypsin, heparin, and acetylcysteine, all without much success. In 1960, Jose Ramirez-Rivera first described the process of physically removing the proteinaceous material by "segmental flooding" of the alveoli. The procedure involved placing a percutaneous transtracheal endobronchial catheter blindly and instilling a small volume (50–100 ml) of saline solution containing heparin, acetylcysteine, or sodium iodide. This triggered a cough, and the patients expectorated a small quantity of milky-white fluid. This was performed four times a day for several weeks while changing the patient's physical position to direct the instilled fluid into different segments. Segmental lavage was shown to improve symptoms, but the procedure was time consuming and was poorly tolerated by the patients. Dr. Ramirez-Rivera continued to improvise on the procedure and, in 1965, introduced "whole-lung lavage." The technique involved intubating the patient with a double-lumen Carlens bronchospirometry tube under general anesthesia, ventilating a single lung while filling the other lung with normal saline containing heparin or acetylcysteine. A total of 1.3–1.8 L of fluid was used to fill the lung over 10 min; patient was then allowed to ventilate normally. Part of the lavage fluid was then drained by gravity, which was followed by vigorous ventilation of the lung. Suctioning was then performed to drain out the milky-white effluent, and the patient was recovered from anesthesia. Following the initial description of the technique, multiple case reports and case series established the safety of the procedure, and sequential whole-lung lavage became the standard treatment in patients with PAP. Over the last five decades, the technique has undergone a few changes; WLL now involves larger fluid volumes, use of normal saline alone without heparin or acetylcysteine, and the routine use of chest percussion during the procedure.

Indications for Whole-Lung Lavage

In early publications in the 1960s, WLL was performed in patients with PAP, chronic asthmatic bronchitis with mucus plugs, and unresolved bacterial pneumonias. Current literature supports the use of WLL in the following conditions:

1. Pulmonary alveolar proteinosis
   Pulmonary alveolar proteinosis is a rare disease characterized by accumulation of surfactant components in the

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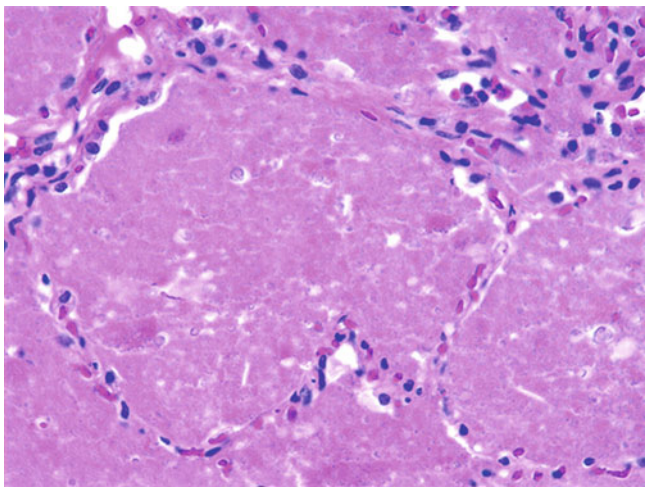

Fig. 71.1 Histology of PAP. Well-preserved alveoli with the accumulation of amorphous lipoproteinaceous material that stains *pink* with periodic acid-Schiff stain and a distinct absence of inflammatory cells

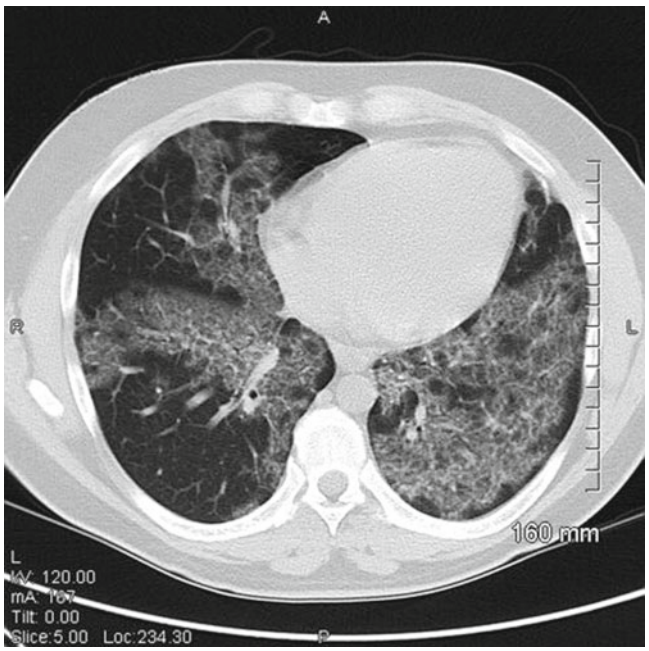

Fig. 71.2 CT scan image of PAP. Patchy areas of ground glass with thickening of the interlobular septa creating a "*crazy-paving*" pattern

alveoli with minimal to no inflammation. If left untreated, PAP results in impaired gas exchange, progressing in some cases to respiratory failure. Congenital, acquired, or secondary causes can to lead to PAP. The acquired form of PAP is more common and is seen in adults, where a circulating antibody to granulocyte-macrophage colony-stimulating factor (GM-CSF) causes a reduction in GM-CSF activity in the lung. This leads to impairment in degradation of surfactant by the alveolar macrophages, which are dependent on GM-CSF. In the congenital form of PAP, genetic mutations result in abnormal surfactant proteins or defective GM-CSF receptors. Secondary PAP is seen in patients with lysinuric protein intolerance, acute inhalational exposures (silica, cement dust, aluminum dust, or titanium dioxide), immunodeficiency disorders, and myeloid leukemias. Irrespective of the etiology, the common endpoint is the accumulation of PAS-positive acellular material in the alveoli (Fig. 71.1) that causes the characteristic "crazy-paving" pattern of ground-glass opacities and septal thickening seen on chest computed tomography scans (Fig. 71.2). In PAP, WLL is indicated when the patients progress to severe dyspnea and hypoxia at rest or with activity, resting PaO_2 less than 65 mmHg at sea level, A-a gradient greater than or equal to 40 mmHg, or measured shunt fraction greater than 10–12 %.

2. Inhalational lung toxicities
   Case reports have suggested WLL as a therapeutic option in inhalational lung injuries, predominantly occupational lung disorders with diffuse pulmonary damage. In these situations, WLL is aimed at removing the mineral dust that cannot be otherwise eliminated by the body. Whole-lung lavage has been performed in patients with exogenous lipoid pneumonia, acute silicosis, lung injury from inhaled plutonium oxide, and pneumoconiosis. Long-term benefits of WLL in these situations are unknown.

Effects of WLL

Beneficial effects of WLL are well established in case series of patients with PAP. Although no criteria to measure adequacy of response are established, 84 % of the patients have a significant clinical, physiologic, and radiologic improvement following WLL. Patients who undergo WLL at any time during the course of their disease have a survival benefit when compared to those who do not undergo the procedure (Fig. 71.3). Studies that compare pulmonary parameters (PaO_2, A-a gradient, DL_{co}, vital capacity, pulmonary shunt fraction) before and after performing WLL have shown a significant improvement with the procedure. The median duration of benefit following WLL is 15 months, and approximately two-thirds of the patients will require a repeat lavage, usually within 6–12 months.

Procedural Considerations

1. Equipment
   Lavage is performed with 15–20 L of sterile normal saline, and the fluid is run through a blood warmer to maintain adequate core body temperature. We also

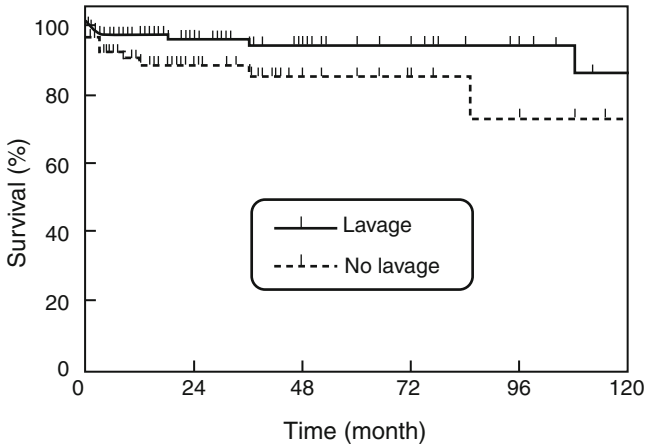

Fig. 71.3 Overall survival from the time of diagnosis of acquired PAP was significantly improved if patients had received therapeutic lavage at any time during their disease course (lavage, n = 146; no lavage, n = 85; $p = 0.044$) (Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis progress in the first 44 years. Am J Respir Crit Care Med. 2002;166:215–35. Official Journal of the American Thoracic Society)

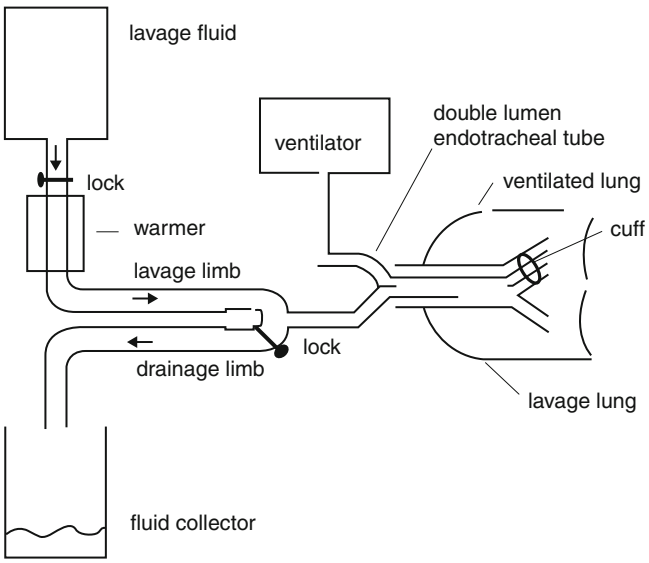

Fig. 71.4 Whole-lung lavage equipment and setup. The lavage fluid is hung in multiliter bags from an IV pole and run through a warmer. A lock is located between the lavage fluid and warmer to control the volumes and timing of the lavage fluid being instilled. The dependent lung is ventilated, while the other is being lavaged. The lavage and drainage limbs are in continuity with the lavage lung only. There is a lock in the drainage limb to control the timing of drainage into the fluid collector

recommend a warming blanket (Bair Hugger; Arizant, Inc., Eden Prairie, MN) covering the exposed body surface to prevent hypothermia, given the prolonged duration of the procedure. Tubing that is generally used for intravenous fluids is connected via an adapter to the double-lumen endotracheal tube to form the inflow and the outflow limbs. Flow through the tubing is controlled with stopcocks. A thin bronchoscope that can be used through the double-lumen endotracheal tube to verify tube position or aspirate secretions should be available at patient's side. Multiple drainage receptacles are needed to collect the effluent. Anesthesia team that is comfortable with intubation with a double-lumen endotracheal tube and single-lung ventilation is required for the procedure.

2. Procedure

   General anesthesia is recommended for the procedure. The patient is initially placed on their back on the operating table and intubated with a double-lumen endotracheal tube. Flexible bronchoscope is used to confirm the tube placement. The bronchial and the tracheal balloons are inflated to isolate the lungs, and double-lung mechanical ventilation is initiated. The patient is then turned to a lateral decubitus position, with the lung being lavaged up in the nondependent position. Meticulous care should be taken to avoid ischemic complications to the extremities by placing supporting pillows in the axilla, under the head, and between the thighs. The position of the endotracheal tube should be reconfirmed. Lung isolation is confirmed by immersing the end of each lumen of endotracheal tube in water and observing for air bubbles while ventilating the other lung. Single-lung ventilation is then initiated, and the tube to the lung to be lavaged is opened to the atmosphere and allowed to deflate. The limb of the double-lumen endotracheal tube that is open to the lung to be lavaged is then connected to the normal saline reservoir (Fig. 71.4). Prior to filling the lung with the fluid, sufficient time should be given to confirm adequate oxygenation while ventilating a single lung.

   With the patient in reverse Trendelenburg position (head end slightly elevated), warm (37 °C) normal saline is allowed to flow freely into the treated lung through the endotracheal tube limb. After allowing 1 L of fluid to run, the tubing is clamped. The patient is tilted into a flat position, and percussion of the lung is performed for approximately 4–5 min. The patient is then tilted into a Trendelenburg position (feet elevated), and the clamp on the outflow tube is released to drain the effluent by gravity into a receptacle. When the flow diminishes, the outflow tube is clamped, the patient is placed in reverse Trendelenburg position, and another liter or warm normal saline is allowed to flow into the lung, and the process is repeated. The initial effluent is milky in appearance that tends to settle on standing. After 10–15 lavages, the fluid becomes progressively less opaque, and when it is clear, the procedure is terminated. Residual saline in the lung is aspirated, and double-lung ventilation is resumed. The input and output of the lavage fluid is carefully charted to prevent excessive residual fluid in the lung. A video

featuring the procedure is available for viewing at http://chestjournal.chestpubs.org/site/misc/videos/media1/index.html.

3. Postprocedure
   The patient is repositioned onto the back and if stable, extubated in the operating room. Otherwise, the double-lumen endotracheal tube is exchanged for a single-lumen tube, and the patient is transferred to the recovery area. Patients can be safely extubated within 24 h, in most cases. In patients with bilateral disease, we prefer to lavage the contralateral lung in 24–48 h, although bilateral sequential whole-lung lavage in the same treatment session can be performed in stable patients.

   A chest radiograph is performed after the procedure to evaluate for complications such as pleural effusion or a pneumothorax. A pleural drain may be necessary, especially if treatment of the contralateral lung is planned, to prevent intraprocedural decompensation of the patient.
4. Complications
   Whole-lung lavage is tolerated well in most patients. The common complication is intraoperative refractory hypoxia which tends to be more of an issue during the lavage of the first lung. Low oxygen saturation (70–80 % range) is not uncommon, especially at the onset of the procedure. This tends to improve spontaneously without any additional interventions. Care should be taken to avoid spillage of lavage fluid into the dependent lung that is being ventilated, which can contribute to hypoxia. If necessary, the positioning of the double-lumen endotracheal tube should be reconfirmed with a bronchoscope, and any visible lavage fluid in the lung being ventilated should be suctioned clean. If required by the severity of hypoxia, hyperbaric oxygen, cardiopulmonary bypass, and extracorporeal membrane oxygenation may be utilized.

   Other complications include pleural effusion, pneumothorax, or hydropneumothorax on the treated side. These can be avoided with meticulous charting of the infused saline and the output and by taking care not to allow instilled fluid to exceed the fluid drained by more than a few hundred milliliters in consecutive lavages.

Conclusion

Whole-lung lavage is a safe and an effective procedure in the treatment of PAP. Although research is underway to develop alternatives such as GM-CSF administration in patients with acquired PAP, WLL remains the cornerstone of management in symptomatic patients with all forms of PAP. Most patients with PAP will eventually require WLL, and a majority of them will need a repeat procedure during the course of the illness.

Complications from the procedure are minimal, especially when performed in centers with adequate resources and experience with single-lung ventilation.

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