Tracheal and Bronchial Surgery

Honorary Editors: Douglas E. Wood, Douglas J. Mathisen, Erino Angelo Rendina

Editors: Xiaofei Li, Federico Venuta, David C. van der Zee

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Tracheal and Bronchial Surgery (FIRST EDITION)

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We are pleased to announce that the "AME Research Time Medical Book Series" co-launched by AME Publishing Company, Central South University Press and DXY.cn will be published as scheduled.

Finishing my medical degree after 4 years and 3 months of study, I decided to quit going on to become a doctor only after 3 months of training. After that, I had been muddling through days and nights until I started engaging in medical academic publishing. Even 10 years after graduation, I had not totally lost the affection for being a doctor. Occasionally, that subconscious feeling would inadvertently arise from the bottom of my heart.

In April 2011, Mr. Tiantian Li, the founder of DXY.cn, and I had a business trip to Philadelphia, where we visited the Mütter Museum. As part of The College of Physicians of Philadelphia, the museum was founded in 1858 and has now become an exhibition hall of various diseases, injuries, deformities, as well as ancient medical instruments and the development of biology. It displays more than 20,000 pieces of items including pictures of wounded bodies at sites of battle, remains of conjoined twins, skeletons of dwarfs, and colons with pathological changes. They even exhibited several exclusive collections such as a soap-like female body and the skull of a two-headed child. This museum is widely known as "BIRTHPLACE OF AMERICAN MEDICINE". Entering an auditorium, we were introduced by the narrator that the inauguration ceremony of the Perelman School of Medicine at the University of Pennsylvania would take place there every year. I asked Mr. Li, "If it was at this auditorium that you had the inauguration ceremony, would you give up being a doctor?" "No," he answered.

In May 2013, we attended a meeting of British Medical Journal (BMJ) and afterwards a gala dinner was held to present awards to a number of outstanding medical teams. The event was hosted annually by the Editor-in-Chief of BMJ and a famous BBC host. Surprisingly, during the award presentation, the speeches made by BMJ never mentioned any high impact papers the teams had published in whichever prestigious journals over the past years. Instead, they laid emphasis on the contributions they had made on improving medical services in certain fields, alleviating the suffering of patients, and reducing the medical expenses.

Many friends of mine wondered what AME means.

AME is an acronym of "Academic Made Easy, Excellent and Enthusiastic". On September 3, 2014, I posted three pictures to social media feeds and asked my friends to select their favourite version of the AME promotional leaflet. Unexpectedly we obtained a perfect translation of "AME" from Dr. Yaxing Shen, Department of Thoracic Surgery, Zhongshan Hospital, Shanghai, who wrote: enjoy a grander sight by devoting to academia (in Chinese, it was adapted from the verse of a famous Chinese poem).

AME is a young company with a pure dream. Whilst having a clear focus on research, we have been adhering to the core value "Patients come first". On April 24, 2014, we developed a public account on WeChat (a popular Chinese social media) and named it "Research Time". With a passion for clinical work, scientific research and the stories of science, "Research Time" disseminates cutting-edge breakthroughs in scientific research, provides moment-to-moment coverage of academic activities and shares rarely known behind-the-scene stories. With global vision, together we keep abreast of the advances in clinical research; together we meet and join our hands at the Research Time. We are committed to continue developing the AME platform to aid in the continual forward development and dissemination of medical science.

It is said that how one tastes wine indicates one's personality. We would say how one reads gives a better insight to it. The "AME Research Time Medical Books Series" brings together clinical work, scientific research and humanism. Like making a fine dinner, we hope to cook the most delicate cuisine with all the great tastes and aromas that everyone will enjoy.

Stephen Wang
Founder & CEO,
AME Publishing Company

Tracheal and bronchial surgery is one of the most recent areas of development in surgery, with techniques being refined in parallel with other modern surgical innovations in open heart surgery and solid organ transplantation. Conditions involving the central airways are uncommon, but not rare, and until relatively recently were managed only with palliative techniques - radiation for malignant disease and permanent airway appliances for benign disease. Pioneering work involved several surgeons worldwide, with major advances in technique and indications developed by Dr. Hermes Grillo in Boston and Dr. F. Giffith Pearson in Toronto. Techniques developed and refined by Drs. Grillo and Pearson, along with others, for the first time allowed patients with life limiting central airway pathology undergo definitive surgical management with expectations of a cure combined with a good quality of life.

Primary tracheobronchial pathology includes tumors, benign strictures, inflammatory processes, congenital abnormalities, and rare primary anatomic variations. The techniques of resection allow definitive surgery with curative intent for tumors, and complete correction of many, but not all, benign strictures. Because these conditions are uncommon, most surgeons do not have the benefit of substantial experience or expertise in central airway surgery, and many patients may still not be offered surgery due to lack of training, concern about potential life-threatening complications, or lack of access to a surgeon with airway surgery experience.

The principles of airway surgery have also created substantial advances in the surgical management of thoracic malignancies with secondary airway involvement. By far the most common is lung cancer. Bronchoplastic techniques now allow sleeve lobectomy for central lung cancer, sparing uninvolved lung parenchyma with improved short and long-term outcomes compared to pneumonectomy. The preservation of pulmonary function allows surgery for many patients who would have otherwise been excluded due to poor pulmonary reserve. These techniques have even extended to carinal resection for certain T4 lung cancers that were previously considered inoperable. Thyroid cancer and some mediastinal tumors with airway involvement may now be considered for complete resection.

In spite of these advances, many patients with central airway pathology may not be candidates for curative or corrective surgery due to longitudinal or radial extent of disease. Airway surgeons should also be experts in interventional bronchoscopy which provides initial palliation of obstructive symptoms while preparing a patient for surgery, as well as providing longer term palliation when resection is not possible. Experience with bronchoscopic dilatation, core-out, laser, and stents is also valuable in managing airway complications that may occur after tracheobronchial resection and reconstruction.

The editors of this text have assembled an incredible wealth of surgical principles, lessons learned, and promising techniques from world experts in tracheal and bronchial surgery. The contributors to this text are the surgical leaders from around the world who have further perfected the management of central airway pathology, and have extensive experience in tracheal and bronchial resections. They also provide a window to further advances in the field that include tracheal replacement and 3D printing to improve management of tracheobronchial malacia. We are fortunate to have such a superb collection of expertise and a virtual encyclopedia of airway management collected in a single volume for easy reference to those caring for patients with life-limiting airway pathology.

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Problems affecting the airway are uncommon. Because of this, it was one of the last areas of surgery to draw the attention of many surgeons.

Tracheobronchial surgery used to be confined to a small number of surgeons who were intrigued by the problems, new concepts, myths, and challenges. The limits of resection and technique of reconstruction were the surgical challenges and anesthesia allowing open airway surgery had to be addressed as well.

The early pioneers identified these issues and tested their hypotheses in the lab and brought the successful ideas to the bedside. This sound, rational approach is still a model for surgical investigation. Trying something before technical details are worked out has too often led to poor patient outcomes. A rush to print before analysis and careful follow up has led to many misadventures and again poor outcomes.

This book promises to be an important contribution and reference for contemporary surgeons interested in airway disease. The number of interested surgeons has expanded around the globe as witnessed by the diverse countries of origin of the contributors.

So as not to forget the origins of this discipline and repeat the mistakes of the past, an historical perspective of tracheal surgery is included. The diverse perspectives provided allow the reader the opportunity to see there is more than one way to do things.

Surgeons continue to push the boundaries by going from large open operations to now where even the most complicated operations have been accomplished by uniportal minimally invasive techniques.

The anesthetic challenges have been met as well. This book addresses techniques that heretofore were thought to be impossible. The use of cardiopulmonary bypass and ECMO have opened new possibilities. The notion that open airway surgery could be done without intubation seemed like an impossibility and yet even that boundary has been crossed.

Readers will enjoy this compilation of interesting reports about surgery of the trachea and bronchi and after reading continue to push the boundaries even further.

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The issue of the present textbook is tracheal and bronchial surgery. This stimulating field of thoracic surgery represents a major technical challenge that has registered a significant improvement over time, thus changing the modern approach to a number of benign and malignant diseases. Outlook for cure of benign tracheal and laryngotracheal stenoses and of tumors involving the airway has dramatically improved in recent years together with growing experience and progressive diffusion of reconstructive techniques.

The progress of such attractive reconstructive procedures has provided new successful results and solutions to clinical problems long remained unsolved. This was made possible largely by improving anesthesia technique; for this main reason a section of this book is dedicated to this aspect.

Lesions affecting the trachea are quite uncommon and only few centers worldwide have collected large experience in this setting. From the first tracheal resection, significant improvement in surgical technique has been made in the last decades; thus offering a chance for definitive cure even to patients with benign subglottic stenosis, for whom palliative procedures had been the rule for a long time. Technical aspects and results of some of the pilot experiences with prosthetic tracheal replacement have been also included in this volume.

Airway reconstructive procedures have also radically modified the surgical management of tumors invading the carina and main bronchi. Increased expertise and acceptance of these techniques have allowed to enlarge the spectrum of operable tumors and to standardize healthy lung parenchyma sparing in the treatment of many patients with centrally located neoplasms. Progressive affirmation of minimally invasive approaches has become a current trend also in this field of thoracic surgery, as proved by the initial experiences reported with video-thoracoscopic or robotic sleeve resections. Interesting chapters by eminent colleagues discussing the role of the latter approaches in such complex operations are part of this volume.

Special attention has been dedicated to technical details of anastomotic reconstruction including those concerning lung transplantation, and to risk evaluation. Judgment and technical accuracy are the way to gain excellent results and to not jeopardize the cure; tip and tricks and new techniques that pertain in particular the prevention and treatment of complications are illustrated.

Endoscopic treatment has a crucial role in the management of airway diseases. Clinical judgment and large specific experience is essential to define the correct indications for such procedures. Operative endoscopy should be considered an additional resource for surgery allowing to improve results of treatment and to avoid unnecessary operation.

This volume offers contributions from some of the main experts in airway disease and surgery with the aim of improving knowledge and providing a guide for surgeons and physicians facing clinical airway problems. We thank all the authors who have contributed to this book. We are convinced that their outstanding support will offer a comprehensive overview of the state of the art of this complex and fascinating topic.

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"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change." – Charles Darwin, 1809.

In 1950, Dr. Belsey wrote that "the intrathoracic portion of the trachea is the last unpaired organ in the body to fall to the surgeon, and the successful solution of the problem of its reconstruction may mark the end of the 'expansionist epoch' in the development of surgery" (Belsey R. Resection and reconstruction of the intrathoracic trachea. Br J Surg 1950;38:200-5.). However, the long segment of trachea resection and reconstruction continues to be a big problem for surgeons until now. Surgery of the trachea and bronchi still represents the most challenging operation for every thoracic surgeon in the world.

Fortunately, we are the one most responsive to change. During the past few decades, the techniques and principles of tracheal and bronchial operations have been shared and disseminated through the world, and the success rate of treatment for tracheal and bronchial diseases has been greatly improved. At the same time, great efforts have been made to simplify the procedures of tracheal and bronchial surgery, to overcome the limit of trachea resection (6cm or half of the trachea), and to explore the new substitute of airway.

This book not only includes the anatomy, basic techniques and classic concept of trachea and bronchi surgery but also introduces the new advance in the repair, reconstruction and replacement of trachea and bronchi such as VATS or robotic technique, 3D printing technique, and so on. This book might provide readers with the basic knowledge, the experience, and the perspective of trachea and bronchi surgery.

It is hoped that this book could inspire more thoracic surgeons to be devoted to change, and to end "the 'expansionist epoch' in the development of surgery".

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Disorders involving the airway are relatively uncommon; adequate treatment planning requires technical skills and experience. For this reason, without a special interest it could be difficult for most individuals to gain adequate competence in this field, where the difference between success and failure may be minimal but makes a big difference. This is particularly true for patients with tracheal problems: in these cases, success means freedom from the need of a lifelong tracheostomy and preservation of the voice. Notwithstanding the first tracheal resection was performed more than 100 years ago, only during the last 30 years an extensive work led to success starting from experiments in the animal lab; details on anatomy, extent of resection, anastomotic tension limits, anastomotic technique and materials resulted in successful treatment of trachea-bronchial disorders.

This book is dedicated to surgery of the airway; enclosed are manuscripts that, starting from the historical perspective, address all the major problems of the airway and their optimal treatment. Advanced techniques are described, from operative endoscopy to tracheal transplantation, from laryngotracheal resection to the anastomotic techniques during lung transplantation, giving a fantastic overview of this technically demanding surgical arena.

We hope that our colleagues familiar with these problems will enjoy the reading; for those that are not yet familiar with them, we hope that they will find the information as an inspiration to gain experience and become leaders in this field.

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This book is a compilation of recently published related articles on the progress of management of airway surgery in the academic arena and covers the complete field of trachea and bronchus surgery. It is a standard work for academics, physicians and medical students, interested in the field of airway surgery.

There is an extensive description of the anatomy enlivened with colourful pictures and artful sketches. The book covers the whole spectrum of management of obstructions, whether by foreign bodies, infectious diseases or malignant tumours. Also the treatment of pediatric patients is included in this extensive works. Surgical techniques varying from simple endoscopic biopsies to complete tracheal replacement will pass in review. There are reports of both open and thoracoscopic approaches for airway management. Also anesthesiological aspects and treatment and prevention of complications after airway surgery are discussed. Finally the book contains a chapter on new techniques and future developments for airway surgery.

Each chapter discusses the most recent advances in management of airway disease and contains an extensive overview of the most recent literature.

We wish to thank all authors for their effort at achieving the highest standards with their contribution. The book warrants its presence in every bookcase.

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This is no ordinary textbook. It is a compendium of recently published articles by this publisher, chosen because of their relevance to the highly focused topic of surgery of the airways. As such it is essentially an encyclopedia providing a worldwide perspective on a subject which is highly relevant, but not always familiar, to the practicing thoracic surgeon. I have no doubt that even the most highly experienced airway surgeons will find this volume both useful and enlightening, as it presents experience from many countries having different geographic, epidemiologic, and socioeconomic differences, affecting the nature, presentation and management of diseases and conditions which can involve the upper airways.

Even in the modern era of rapid transmission of new knowledge and the ability to instantaneously search worldwide references, familiarity with the knowledge and experience from other parts of the world is often limited. I am reminded of an experience I had in 1981 when, as a guest of the Soviet Union, I presented our experience at the Toronto General Hospital, using the median sternotomy approach for bilateral pulmonary procedures for both benign and malignant conditions. When asked afterward by famous senior Russian thoracic surgeon if we had done many such procedures I summoned what little modesty I may have had and said "We have done almost 20 cases." His response to me was, "We have done almost 1000 cases". I have no doubt as to his veracity and remember the feeling of embarrassment that I knew so little regarding the experience, and literature from other countries. Even now our awareness of new information may be circumscribed and the editors of this text are to be congratulated for compiling this valuable global resource.

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"The LORD God formed the man from the dust of the ground and breathed into his nostrils the *breath of life*, and the man became a living being" (Genesis 2:7). According to Wikipedia, "Breath of Life" is a song by the English indie rock band Florence and the Machine, recorded exclusively for the film *Snow White and the Huntsman* (2012). The song received many positive reviews from music critics (1).

This textbook "*Trachea and Bronchus Surgery*" edited by X. Li and F. Venuta is a state of the art review meant for thoracic surgeons dealing with diseases of the airway. Most chapters are written by experts in the field of tracheal and bronchial surgery. The book covers all surgical aspects for successful treatment of airway pathology: from history, to diagnosis, anaesthesia, resection and reconstruction, endoscopic management, treatment and prevention of complications, and new and evolving techniques such as tracheal replacement and tracheal engineering. The entire spectrum of diseases of the airways are discussed: diverticulum, stenosis, benign and malignant tumors, foreign bodies, trauma, infectious disorders, fistula.

This textbook is a very welcomed reference work for thoracic surgeons interested in the many aspects of airway pathology and its management. The late Hermes C Grillo (1923-2006) and F. Griffith Pearson (1926-2016), both pioneers in airway surgery, would have been very be proud to read this publication and to write this preface.

We are gratefull to all authors for teaching us how to keep the airway open so that the *breath of life* can be blown again into any individual suffering from an airway disorder. By following the principles written in this book, our patients will remain living human beings.

References

1. Breath of Life. Available online: https://en.wikipedia.org/wiki/Breath_of_Life_(Florence_and_the_Machine_song). [Accessed November 1, 2017].

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Airway surgery represents a challenging field for the thoracic surgeon. This subspecialty has found development only after the second half of the 20th century, thanks to the work of pioneers, who first decided to study this organ's anatomy and physiology, and developed specific surgical techniques to perform tracheal and bronchial resection and reconstruction. Merit of these outstanding surgeons does not only lie in their clinical achievements, but also in their life-long effort in teaching and sharing their experience to thoracic community, by the aid of textbooks and papers, that have become milestones of the scientific literature.

Today, such procedures as tracheal resection and anastomosis, repair of tracheo-esophageal fistulas, tracheal and bronchial sleeve resections and lung transplantation are considered an integral part of thoracic surgery, although these remain challenging operations, reserved to a relatively restricted number of specialized centers over the world.

Furthermore, a growing surgical expertise, newer technical advances, development of biomaterials, and the rise of minimally invasive thoracic surgery, have added complexity to the panorama of airway surgery, broadening the spectrum of possible therapeutic interventions.

With this premises in mind, this book aims to offer the most up-to-date knowledge on the subject, from the most authoritative experts around the globe. All the many facets of this fascinating discipline are covered and discussed in-depth, including its most recent developments.

I deeply recommend this manual as a textbook for anyone who wants to approach tracheal and bronchial surgery for the first time, as well as a state-of-the-art reference volume for all physicians already involved in this field.

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Surgical anatomy of the tracheobronchial tree

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Abstract: Airway surgery is often indicated in the management of benign or malignant pathological processes of the tracheobronchial tree. The surgeon undertaking this type of work has, however, the responsibility of understanding the particular anatomy applicable to these structures and procedures as well as be able to correlate imaging, intraoperative findings and anatomy. These are important considerations if one wants to reduce operative morbidity and improve potential for better long-term results. This paper reviews the most important anatomic features of the tracheobronchial tree putting emphasis on those features that are important to surgeons performing surgical procedures on those organs.

Keywords: Anatomy; tracheobronchial tree; surgery of the tracheobronchial tree

Introduction

In the preface of his "de Humani Corporis Fabrica", Andreas Vesalius [1514-1564] wrote that anatomy should rightly be regarded as the firm foundation of the whole art of medicine. This observation is even more pertinent to the art of airway surgery, in which safe techniques are largely dependent on optimal knowledge of normal anatomy and of its variants. Surgeons undertaking subglottic or tracheal resections must, for instance, be familiar with the particular anatomic arrangements of these structures as well as of their blood supply and innervation if they want to avoid improper operations or technical mishaps. Indeed, the essential facts of anatomy must be well known if one wants to insure that each patient gets the best possible operation for his or her airway disorder.

Anatomy of the glottis and subglottic regions

The glottis and subglottis extend from the vocal cords above to the lower border of the cricoid cartilage below. The glottis includes the vocal cords together with the anterior and posterior commissures while the subglottic region extends from a plane approximately 1 cm below the free margin of the true vocal cords to the lower border of the cricoid cartilage (1).

Surgery on the glottis and subglottis is complex not only because it is carried out in close proximity to the vocal cords but also because complete transection of the subglottic airway at any level above the cricothyroid joint will invariably result in the division of the recurrent laryngeal nerves with resultant vocal cord paralysis. In addition, the posterior rim of the upper border of the cricoid cartilage supports the arytenoid cartilages which play a critical role in vocal function (2).

Descriptive anatomy

The rigid framework of the larynx is provided by nine cartilages joined by intercartilaginous membranes (*Figure 1*).
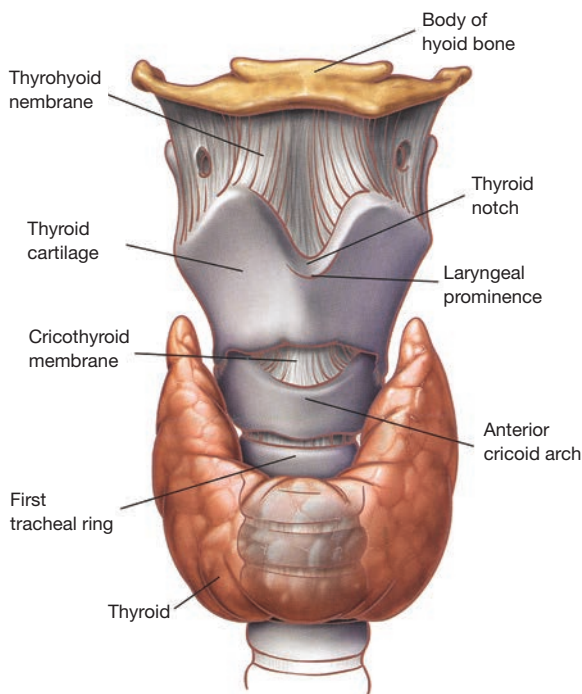
Figure 1 Anterior view of the laryngeal cartilages and membranes (courtesy from Dr. Jean Deslauriers and reproduced from Deslauriers J: Anatomy of the neck and cervicothoracic junction. Thorac Surg Clin 2007;17:530).

Table 1 Extrinsic musculature of the larynx
Muscles that elevate the larynx (elevators)
Stylohyoid, digastric, mylohyoid, geniohyoid, stylopharyngeus, thyrohyoid
Muscles that depress the larynx (depressors)
Omohyoid, sternohyoid, sternothyroid

The hyoid bone is not a true component of the larynx but is closely related to it through the extrinsic laryngeal musculature (*Table 1*) (*Figure 2*). While performing a tracheal resection, the larynx has sometimes to be released through the division of these extrinsic laryngeal muscles in order to obtain a tension-free reconstruction (3,4).

The thyroid, cricoid, and part of the arytenoid cartilages are made of hyaline cartilage whereas the other laryngeal cartilages are made of elastic fibrocartilages. With age, hyaline cartilages have a tendency to become ossified, more so and earlier in men than in women.

The thyroid cartilage is the largest of all laryngeal cartilages. Its superior border connects with the hyoid bone
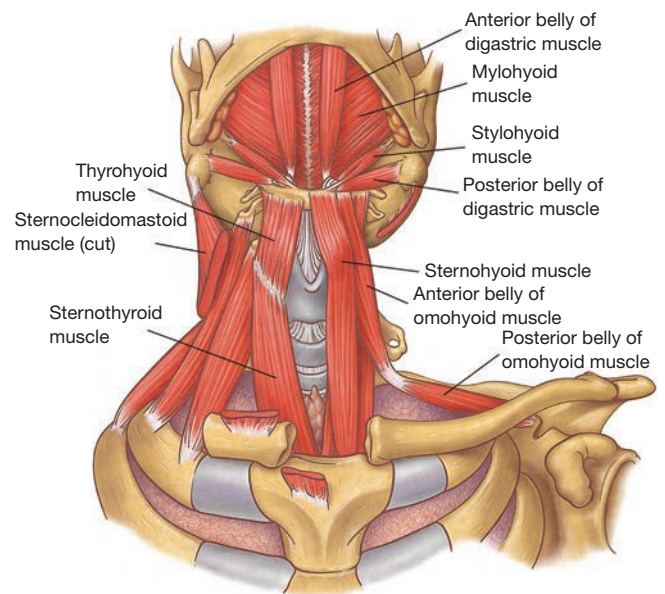
Figure 2 Topography of the extrinsic musculature of the larynx (courtesy from Dr. Jean Deslauriers and reproduced from Deslauriers J: Anatomy of the neck and cervicothoracic junction. Thorac Surg Clin 2007;17:536).

through the thyrohyoid membrane, and its inferior border is attached to the cricoid cartilage through the cricothyroid membrane (*Figure 1*). It is through this thick and relatively avascular membrane that the airway is closest to skin and it is where cricothyroidotomies (coniotomies) are carried out (5).

Over the anterior neck, the laryngeal prominence (Adam's apple) is formed by the angle of union of the two lateral laminae of the thyroid cartilage at the level of C4-C5. Above the laryngeal prominence, the laminae of the thyroid cartilage diverge to create a U-shaped depression called the thyroid notch. From the posterior border of the thyroid cartilage, two slender processes extend superiorly and inferiorly, forming the superior and inferior horns (cornua), respectively.

The cricoid cartilage is the only complete cartilaginous ring of the larynx and also its main supporting structure. It has an anterior arch similar to a normal tracheal ring and a much broader posterior plate or cricoid lamina (*Figure 3*). The lamina has a vertical crest in its midline and two lateral fossae, sites of insertion of the posterior cricoarytenoid muscles which are the primary abductors of the vocal cords. The paired arytenoid cartilages rest on the superior border of the posterior cricoid plate (*Figure 3*) and articulate at the cricoarytenoid joints on the lateral part of the cricoid
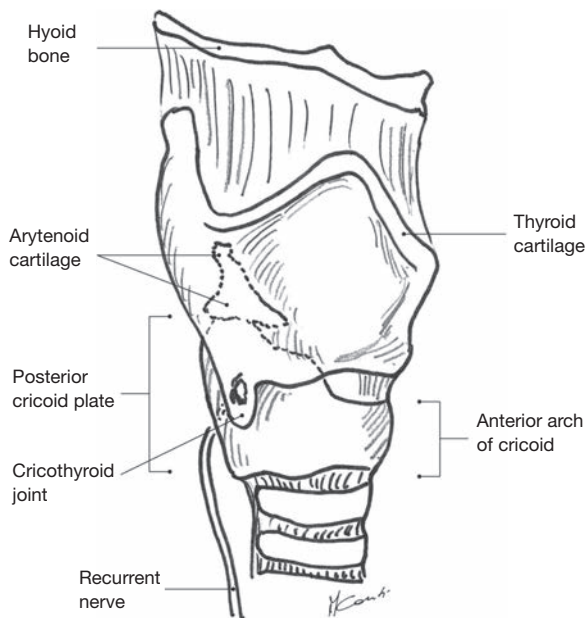
Figure 3 Lateral view showing the pertinent anatomy of the glottis and subglottic regions and of the upper trachea.
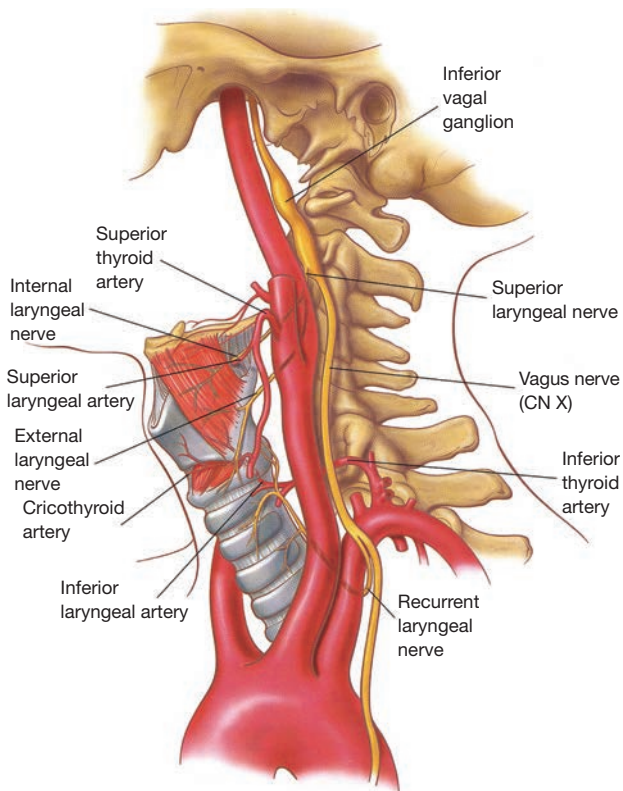
Figure 4 Arterial supply and innervation of the larynx (reproduced from Thorac Surg Clin 2007;17:553 [Deslauriers J, Editor]).

lamina. The vocal cords are attached posteriorly to the vocal processes of the arytenoid cartilages and anteriorly to the thyroid cartilage.

The corniculate and cuneiform cartilages are two small cylindrical or conical cartilages located above the vertex of the arytenoid cartilages in the arytenoepiglottic ligament. These cartilages pull on the epiglottis during swallowing thus contributing to the closure of the laryngeal aditus. The epiglottis is a thin, oval, and flexible lamina located in the superior part of the larynx. Anteriorly, the epiglottis is attached to the hyoid bone through the hyoepiglottic ligament, whereas its inferior end is attached to thyroepiglottic ligament. During swallowing, the superior part of the epiglottis moves backward and contributes to protect the laryngeal aditus from aspiration.

Vascular supply

The vascular supply to the glottis and subglottic airway comes from the superior laryngeal arteries, which are branches of superior thyroid arteries, and from the posterior and inferior laryngeal arteries, which originate from the inferior thyroid artery (*Figure 4*). In contrast to the segmental and highly susceptible to injury blood supply of the trachea, the arterial branches going to the larynx form a rich anastomotic network and thus the larynx is somewhat resistant to ischemia.

The venous drainage of the larynx is through superior and inferior laryngeal veins, which ultimately drain into the internal jugular veins via the thyroid veins. The lymphatics of the glottis drain into the deep cervical nodes, whereas those of the subglottic airway drain into the internal jugular, prelaryngeal, and upper paratracheal nodes.

Innervation

The larynx is innervated by the superior laryngeal nerves and by the inferior or recurrent laryngeal nerves, both branches of the vagus nerves (*Figures 4,5*).

The superior laryngeal nerves (*Figure 4*) divide into an internal branch, which pierces the thyrohyoid membrane and provides sensory function to the supraglottic airway, and an external branch, which provides motor function to the cricothyroid muscles and inferior constrictors of the pharynx as well as sensory function to the vocal cords (6).

At the base of the neck, the right vagus nerve crosses the origin of the right subclavian artery behind the sternoclavicular joint, and gives off the right recurrent
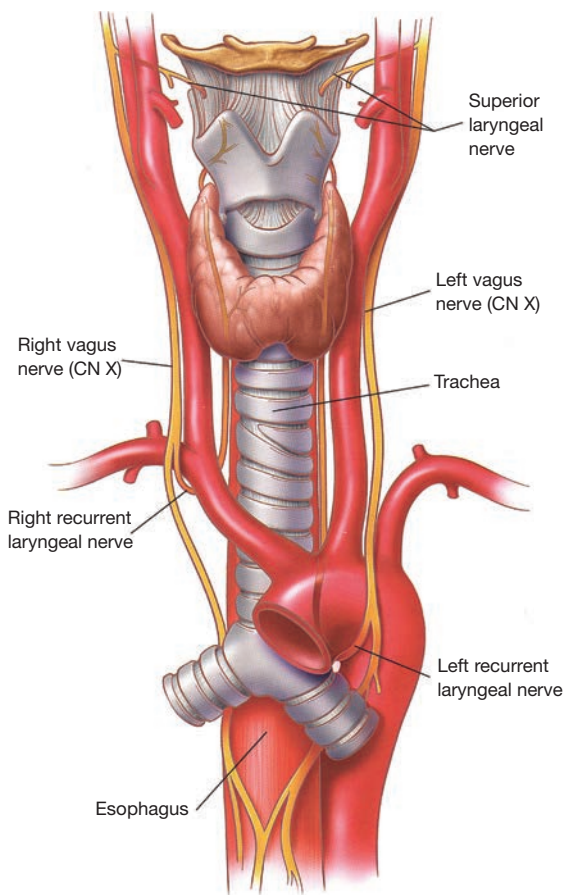
Figure 5 Anatomy of the superior and inferior recurrent laryngeal nerves (courtesy from Dr Jean Deslauriers and reproduced from Deslauriers J: Anatomy of the neck and cervicothoracic junction. Thorac Surg Clin 2007;17:544).

laryngeal nerve (inferior laryngeal nerve) that loops around and under the subclavian artery (*Figure 5*). The right recurrent nerve ascends in the tracheoesophageal groove, where it can be injured during extensive cervicomediastinal dissections sometimes done for malignant neoplasms located near or at the thoracic inlet. On the left side, the recurrent laryngeal nerve originates close to the ligamentum arteriosum in the left chest and courses around the aortic arch from front to back before ascending to the neck in the tracheoesophageal groove.

On each side, the recurrent nerves accompany the laryngeal branch of the inferior thyroid artery behind the cricothyroid articulation (*Figure 4*) and enter the larynx posterior to the inferior horns of the thyroid cartilages. They give off an anterior branch, which innervates all intrinsic laryngeal muscles except the cricothyroid, and

a posterior branch which supplies motor function to the inferior constrictor muscles of the pharynx.

The recurrent laryngeal nerves are susceptible to surgical injury when they enter the larynx next to the cricoid plate behind the cricothyroid articulation. This is the reason why most surgeons believe that partial or total resection of the cricoid cartilage should always be done subperichondrally as to not injure these nerves. Recurrent nerve injury at that level will produce vocal cord paralysis, the end-result of such paralysis being interference with normal phonation, respiration, and sphincteric function (paralysis of interarytenoid muscles), all associated with significant patient morbidity. The technique of subglottic resection described by Pearson and also named the "Pearson Operation" (7), allows transverse division of the airway up to the level of the inferior border of the vocal cords without injuring the recurrent laryngeal nerves.

Anatomy of the trachea

The trachea originates below the cricoid cartilage and extends from front to back to the carina. Until its anatomy and vascular supply were better understood in the late 1960's, it was generally accepted that surgeons could safely remove no more than two or three tracheal rings, "the two centimeter rule", and predictably be able to reconstruct the airway with primary anastomosis. As late as 1990, Professor Andreas (Andy) Naef, a prominent airway surgeon from Switzerland said: "*Tracheobronchial tissue, as compared with the stomach, intestine, or even skin, does not heal well… both the rigidity and the poor blood supply of the cartilaginous structure are definitely major handicaps*" (8). With improved understanding of anatomy and blood supply allowing for better use of mobilization techniques, half the tracheal length can now be safely resected and the airway be primarily reconstructed.

Descriptive anatomy

The trachea is a cartilaginous and membranous tube which is continuous with the larynx at the level of the cricoid cartilage (*Figure 6*). Its uppermost portion is located at the level of the sixth or seventh cervical vertebrae in the neck, while its lower end lies at the level of the fourth or fifth thoracic vertebrae in the chest. In the adult, the tracheal length ranges from 10–13 cm (longer in men than in women) with approximately 5 cm lying superior to the suprasternal notch.

The trachea has an anterior horseshoe-shaped part made
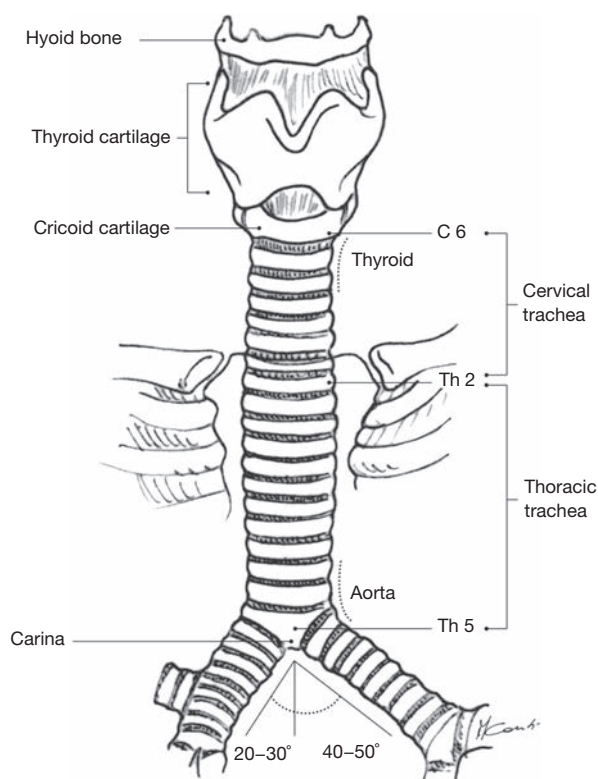
Figure 6 The trachea extends from the cricoid cartilage at the level of C6-C7 to the carina at the level of T4-T5.
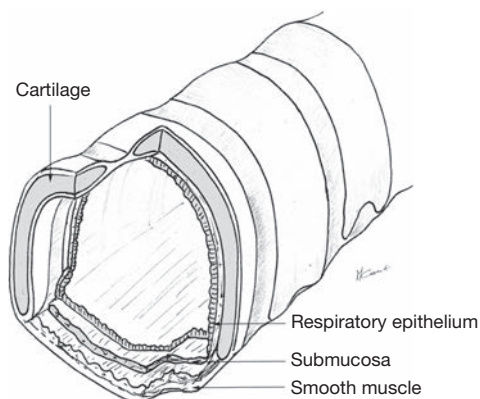
Figure 7 The trachea and main bronchi have an anterior horse-shoe shaped cartilaginous portion and a posterior membranous part.

of 18–22 cartilaginous rings (2 rings per cm of trachea) and a membranous part posteriorly (*Figure 7*). Between the rings anteriorly, the non-cartilaginous tissue is elastic and allows lengthening or shortening of the trachea during respiration. In younger individuals, the trachea is somewhat more

elastic and extensible, while in older people, it is more rigid or even sometimes ossified a significant consideration while doing tracheal resections.

The cross-sectional shape of the trachea can be elliptical (larger transverse than antero-posterior diameter), C-shaped (equal transverse and antero-posterior diameters), or U-shaped (2). In an interesting anatomical autopsy study, Mehta and Myatt showed that the U-shaped trachea was the most common variant in adult men while the elliptical shape was the most common in adult women (9). The human trachea is, however, a dynamic and distensible organ of continuously varying size, shape, and tone.

The posterior membranous tracheal wall consists of an enveloping fibrous sheath with smooth muscle. Both the tracheal cartilages and membranous wall are lined by ciliated pseudo-stratified respiratory columnar epithelium.

From the front view, the trachea is located in the midline, and from the lateral position, it courses backwards and downwards. With the neck fully extended, the trachea is half cervical and half intrathoracic but when the neck is in maximal flexion, the cricoid cartilage can be brought down to the level of the sternal notch and the trachea becomes almost entirely in an intrathoracic position. Thoracic surgeons often maintain maximal postoperative neck flexion in order to minimize anastomotic tension following segmental tracheal resection.

The anterior anatomical relationships of the trachea are those with the thyroid gland in the neck and mediastinal great vessels intra-thoracically. In the neck, the thyroid and thyroid isthmus are in front of the trachea at the level of the second or third tracheal rings while in the mediastinum, great vessels cross the trachea at various levels (*Figure 8*). The innominate artery crosses over the mid-trachea obliquely from its site of origin in the aortic arch and the right and left innominate veins are located anterior to the innominate artery. In young women, the innominate artery is often in a higher location at the base of the neck and can thus be in contact with a tracheal anastomosis done at neck level. This particular anatomical arrangement can sometimes lead to catastrophic postoperative tracheovascular fistulae. The superior vena cava is anterior and to the right of the trachea. Posteriorly, the membranous trachea is in contact with the esophagus on the left and vertebral bodies on the right.

Vascular supply and microcirculation

Because most complications occurring following tracheal

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Drevet et al. Surgical anatomy of the tracheobronchial tree
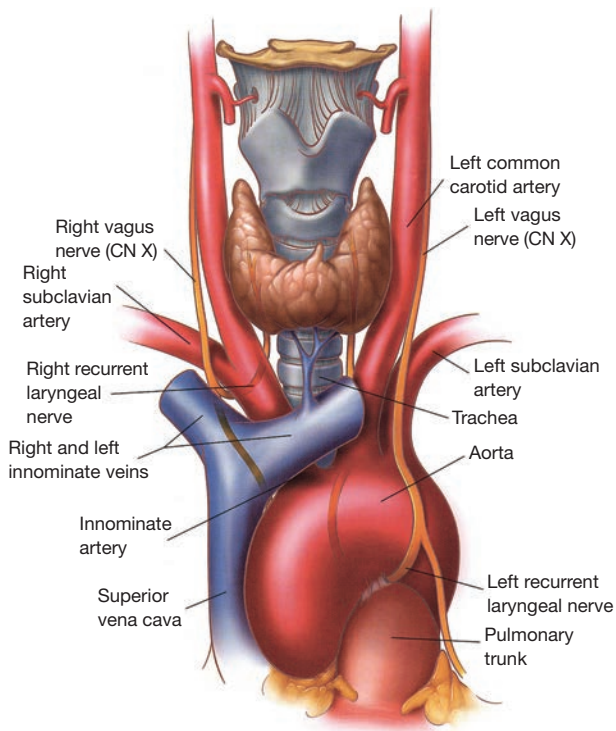
Figure 8 Anatomical relationships of the trachea with surrounding structures [reproduced from Thorac Surg Clin 2007;17:579 (Deslauriers J, Editor)].

Figure 9 Tracheal blood supply [reproduced from Thorac Surg Clin 2007;17:575 (Deslauriers J, Editor)].

reconstruction are related to the disruption of vascular supply at the level of the anastomosis, operating surgeons must have a clear understanding not only of the blood supply to the trachea but also of its segmental nature and longitudinal anastomotic connections.

The inferior thyroid vessels and their tracheoesophageal branches provide blood supply to the proximal trachea while the bronchial arteries vascularize the distal trachea, carina, and main bronchi (*Figure 9*) (10-12). The trachea is also supplied by small branches originating from the subclavian artery, internal mammary artery, and innominate artery. Once they reach the tracheoesophageal groove, the tracheoesophageal branches divide into primary tracheal and primary esophageal branches (*Figure 10*). Tracheal vessels enter the trachea over its lateral wall branching superiorly and inferiorly over the width of several tracheal rings.

Throughout the length of the trachea, there is an extensive submucosal plexus fed by intercartilaginous arteries, each penetrating the soft tissue space between the tracheal rings and running anteriorly (*Figure 10*). As

they reach the midline, these arteries run more deeply and terminate in submucosal capillary plexuses. The tracheal cartilages receive their blood supply from these plexuses while the membranous trachea is vascularized through secondary branches originating from the primary esophageal arteries.

Venous drainage is through the azygos and hemi azygos systems while lymphatic drainage is through the low and high paratracheal nodal chains eventually reaching the deep cervical nodes.

Innervation

The innervation of the trachea comes from tracheal branches originating from the thoracic sympathetic chain and inferior ganglion of the vagus nerve. This innervation is responsible for tracheobronchial muscle tone (bronchoconstriction or bronchodilation), mucous production, and vascular permeability. Afferent vagal fibers are also responsible for sneezing and cough reflex.

Anatomy of the carina and main bronchi

The most inferior portion of the trachea, the bifurcation, is
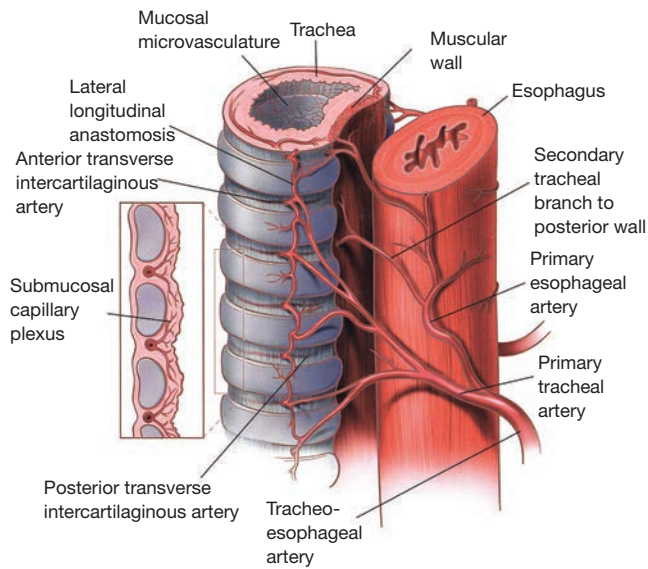
Figure 10 Microscopic blood supply of the trachea [reproduced from Thor Surg Clin 2007;17:578 (Deslauriers J, Editor)].

Figure 11 Anatomy of the carina [reproduced from Thor Surg Clin 2007;17:584 (Deslauriers J, Editor)].

called the carina. It lies slightly to the right of the midline at the level of the fourth or fifth thoracic vertebra posteriorly and sternomanubrial junction anteriorly.

Descriptive anatomy

The tracheal lumen narrows slightly as it progresses toward the carina. The angle between the two main stem bronchi varies among individuals and is generally greater in children than in adults (13). The configuration of the cartilages at the carina is also quite variable.

The right main stem bronchus has a vertical orientation being almost in direct line with the lower trachea (*Figure 11*), and its length from carina to right upper lobe take-off varies between 2.0 and 2.5 cm. By contrast, the left main stem bronchus arises at a more oblique angle and has a more horizontal orientation. The left main bronchus is approximately 4–6 cm long and it travels underneath the aortic arch to reach the posterior left hilum where it bifurcates into upper and lower lobe bronchi. Because of such an anatomical arrangement, the aorta prevents effective mobilization and elevation of the left main bronchus while doing carinal reconstructions. By contrast, the right main bronchus can easily be elevated to the level of the upper intrathoracic trachea for airway anastomosis.

The main anatomic relationship of the carina is that with the right pulmonary artery which lies anterior and inferior

to the carina making it vulnerable to injury during the course of mediastinoscopy. The left pulmonary artery arises considerably more anterior than the left main bronchus when it exits the pericardium underneath the aortic arch.

Vascular supply

Even if some of the vascular supply to the carina comes from the pulmonary arteries, most (90%) of it comes from the bronchial arteries whose level of origin, number, and distribution can be quite variable (12,14,15). More commonly, however, bronchial arteries arise from the antero-lateral aspect of the descending thoracic aorta at the level of the T5 and T6 vertebrae or from intercostal arteries located 2–3 cm distal to the origin of the left subclavian artery. There are usually three bronchial arteries, two on the left side and one on the right side (*Figure 12*).
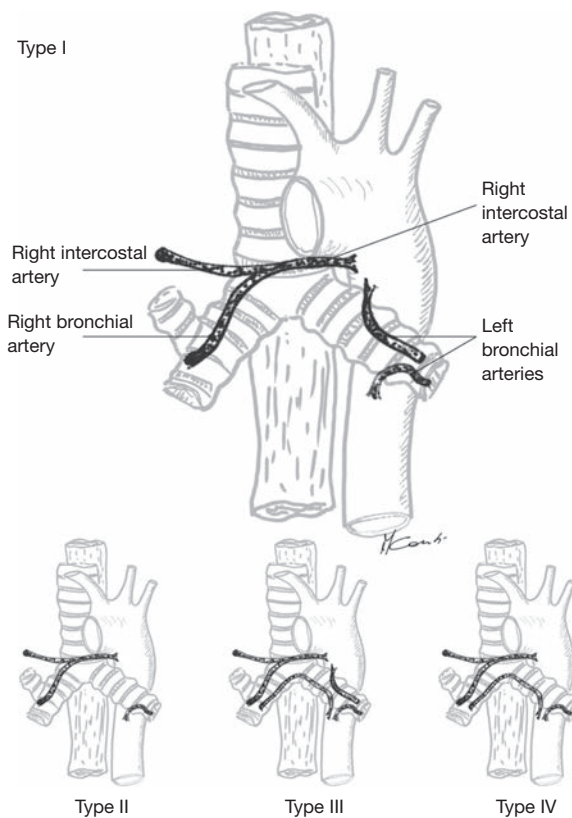
Figure 12 The most common bronchial artery anatomy is one right artery arising from an intercostal artery and two left arteries with separate origins. The inset (bottom) demonstrates the next three most common bronchial artery arrangements.

Proximally, the bronchial arteries circulate posteriorly to the airway where they lie on the membranous portion of main stem bronchi and more distally, they provide vascular supply to the lobar and segmental bronchi. On the right side, the single bronchial artery runs parallel to the azygos vein by which it is overlapped.

Most of the venous drainage from the bronchial arterial system empties into the pulmonary veins although some of it may empty into the azygos and hemiazygos system (16). Lymphatic drainage is through the subcarinal and low paratracheal nodal chains.

Main anatomical variations

There are several known anatomic variations in the tracheobronchial system but their true incidence is unknown owing to their mostly asymptomatic nature. Recognition of these variations may, however, be important

while performing certain procedures such as bronchoscopy, endotracheal intubation, or positioning of lung isolation devices (17).

A tracheal bronchus is typically described as a right upper lobe bronchus originating from the trachea, usually at the junction of the middle and distal thirds. Its prevalence is in the range of 0.1% to 2% and it is often associated with cardiac congenital anomalies such as tetralogy of Fallot or ventricular septal defects. The most serious clinical implication of a tracheal bronchus is that a misplaced endotracheal tube can occlude its lumen resulting in secondary atelectasis, obstructive pneumonia or even respiratory failure (18,19). If unrecognized, accidental intubation directly into a tracheal bronchus can also lead to respiratory failure.

An accessory cardiac bronchus is a supernumerary bronchus most commonly originating from the medial wall of the bronchus intermedius and extending parallel to it toward the mediastinum. Most accessory cardiac bronchi end in a blind pouch (diverticulum), ventilated parenchyma or cystic degeneration. The only clinical implication of an accessory cardiac bronchus is that it can serve as a reservoir for infectious organisms in which case surgical resection could be indicated.

The term "bridging bronchus" is used to describe an airway malformation where the middle and right lower lobes are supplied by an aberrant bronchus originating from the left main stem bronchus and crossing over the mediastinum (17). Patients with this rare condition are often symptomatic, presenting with cough, wheezing or even respiratory distress. Most such patients, however, have associated congenital defects, usually of the cardiovascular system, which ultimately determines their prognosis.

Conclusions

Anatomically, the airway presents several unique features that account for the difficulties in the surgical management of pathological processes originating in those areas. These features include a unique cartilaginous support, its relationship to important surrounding structures, and its segmental vascular supply. It is important that the surgeon operating on the airway understands this particular anatomy, the limits of surgery, and most importantly the steps to be taken to avoid catastrophic complications.

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Footnote

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Rigid bronchoscopy and silicone stents in the management of central airway obstruction

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Abstract: The field of interventional pulmonology has grown significantly over the past several decades now including the diagnosis and therapeutic treatment of complex airway disease. Rigid bronchoscopy is an invaluable tool in the diagnosis and management of several malignant and non-malignant causes of central airway obstruction (CAO) and has become integral after the inception of airway stenting. The management of CAO can be a complicated endeavor with significant risks making the understanding of basic rigid bronchoscopy techniques, ablative technologies, anesthetic care and stenting of utmost importance in the care of these complex patients. This review article will focus on the history of rigid bronchoscopy, the technical aspects of performing a rigid bronchoscopy as well as the use of silicone stents their indications, complications and placement techniques.

Keywords: Rigid bronchoscopy; silicone stenting; central airway obstruction (CAO); ablative technologies

Introduction

Rigid bronchoscopy has been an invaluable tool for over a century in the diagnosis and management of innumerable pulmonary diseases. Since its inception by Dr. Gustav Killian in the late 1800's the use and popularity of this technique has waxed and waned. However, with advances in flexible bronchoscopy, ablative technologies and stenting over the past two decades rigid bronchoscopy has again become an integral tool in the management of malignant and non-malignant central airway disease by thoracic surgeons and interventional pulmonologists.

History of rigid bronchoscopy

Dr. Gustav Killian performed the first rigid bronchoscopy in the late 1800's. This innovative procedure provided

physicians with a new glimpse into human anatomy and sparked the growth of pulmonary medicine. Using a metal tube, a light, and topical cocaine anesthesia, Killian removed a pork bone from a farmer's airway in 1897 (1). Prior to the invention of rigid bronchoscopy, over half of the patients who aspirated foreign bodies died, mostly of a post obstructive pneumonia. Rigid bronchoscopy with foreign body removal quickly evolved into the treatment of choice in these patients, with a clinical success rate above 98% (2). During the early 1900's, Killian published extensively and lectured throughout the world. He further went on to adapt his bronchoscopes, laryngoscopes and endoscopes, and first described techniques such as using fluoroscopy and X-ray to define endobronchial anatomy. The design and functionality of the rigid bronchoscope was improved further in 1904 when Chevalier Jackson, who is regarded as the father of American bronchoesophagology first equipped

his bronchoscope with a suction channel and a small light bulb at the distal tip to provide illumination.

The rigid bronchoscope quickly became an indispensable piece of equipment for otolaryngologists across the world and remained the only medical instrument to access the airways until 1963 when Shigeto Ikeda from the National Cancer Center Hospital in Tokyo, Japan introduced the flexible fiberoptic bronchoscope (3,4). For the next 30 years the use of rigid bronchoscopy declined as flexible bronchoscopy quickly gained worldwide acceptance and almost completely replaced the rigid bronchoscope as the diagnostic instrument of choice for pulmonary disease. In a survey performed in 1989, 8% of responders were performing rigid bronchoscopy (5). In a repeat survey in 1999 this number had declined to only 4% (6).

It was not until the lung cancer epidemic of the late 1900's and the associated increase in central airway obstruction (CAO) that the utility of the rigid bronchoscope reemerged. In addition, recognition of certain advantages that rigid bronchoscopy has over flexible bronchoscopy such as airway control and ventilation during intervention as well as the ability to simultaneously use larger forceps, suction catheters and tumor excision techniques have led to the increase in rigid bronchoscopies being performed today.

Central airway obstruction (CAO)

The majority of rigid bronchoscopies done today are for the diagnosis and management of CAO. CAO is generally split into malignant and non-malignant disease. Malignant disease outnumbers non-malignant disease due to the rising incidence of primary lung cancer as well as countless types of malignancies that can metastasize to the lung (7). Non-malignant causes of CAO are often iatrogenic and secondary to endotracheal intubation or prior tracheostomy as well as inflammatory and connective tissue disorders (8). Although less prevalent, it is important to diagnose and treat these appropriately as patients with non-malignant CAO often have a longer life expectancy and can live with their disease for years to decades, as opposed to their malignant counterparts.

The incidence of CAO is difficult to estimate, but does appear to be on the rise in large proportion due to the increase in primary lung cancer. It is estimated that about 20-30% of patients with primary lung cancer will develop CAO, many of which may benefit from palliative measures to relive dyspnea caused by the obstruction (9). While less prevalent, non-malignant cases also appear to be on the

rise. It is unclear whether this is due to increased availability of bronchoscopy leading to increased discovery versus the increase in ICU care, endotracheal intubation and tracheostomy (8).

The causes of malignant and non-malignant CAO are listed in *Table 1*. Primary tracheobronchial tumors are extremely rare consisting of adenoid cystic carcinomas [600-700 cases per year (10)], bronchial carcinoid tumors which are slightly more common with an incidence of 2 cases per 100,000 globally (11) and primary squamous cell and adenocarcinomas of the trachea. Much more common are metastasis of primary lung cancer, breast, renal cell, melanoma and thyroid cancers.

The anatomy of malignant CAO is generally classified into three groups. The first consisting of tumors that are purely intra-luminal and do not erode outside of the tracheal wall or cartilage. The second category of CAO is extrinsic compression from either parenchymal metastasis or mediastinal adenopathy. Finally, the most common category of CAO is a mixed extrinsic/intrinsic stenosis. These forms of stenosis generally originate outside of the airway and erode into the lumen. Differentiating between these three types of CAO is important as therapeutic options can differ for each category (*Figure 1*).

Non-malignant CAO is most frequently caused by iatrogenic injury post endotracheal intubation or tracheostomy placement. However, inflammatory and connective tissue disorders including Wegener's granulomatosis, sarcoidosis, amyloidosis, relapsing polychondritis and tracheobronchopathia osteochondroplastica can also be the etiology of CAO. Another large category of non-malignant CAO is lung transplantation and stenosis at the anastomotic site. As mentioned previously the treatment intent in malignant CAO is almost always palliative in nature. This is certainly not the intent in many cases of non-malignant CAO where the intent should be curative. Rigid bronchoscopy with dilation and stenting should be used as a trial for improvement in symptomatology and as a bridge to curative surgical repair. Long-term stenting of benign stenotic airways may cause extension of the stenotic area due to granulation tissue, which may actually hinder future surgical repair.

As mentioned above the primary goal for rigid bronchoscopy is to relieve dyspnea and improve quality of life (QOL) caused by CAO in malignant as well as non-malignant disease. There have been a small number of papers published looking at the subjective improvement of dyspnea after bronchoscopy and relief of CAO, the

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Table 1 Etiologies of central airway obstruction

Non-malignant
  Lymphadenopathy
    Sarcoidosis
    Infectious (i.e., tuberculosis, histoplasmosis)
  Cartilage
    Relapsing polychondritis
  Granulation tissue from
    Endotracheal tubes
    Tracheostomy tubes
    Airway stents
    Foreign bodies
    Surgical anastomosis
    Wegener's granulomatosis
  Pseudotumor
    Hamartomas
    Amyloid
    Papillomatosis
  Hyperdynamic
    Tracheomalacia
    Bronchomalacia
  Webs
    Idiopathic
    Tuberculosis
    Sarcoidosis
  Other
    Foreign body goiter
    Mucus plug
    Blood clot
Malignant
  Primary airway carcinoma
    Bronchogenic
    Carcinoid adenoid cystic
    Mucoepidermoid
  Metastatic carcinoma to the airway
    Bronchogenic
    Renal cell
    Breast
    Thyroid
    Colon
    Sarcoma
    Melanoma
  Laryngeal carcinoma
  Esophageal carcinoma
  Mediastinal tumors
    Thymus
    Thyroid
    Germ cell
  Lymphadenopathy
    Associated with any of the above malignancies
  Lymphoma

largest being a multicenter registry study of 947 patients at 23 centers undergoing therapeutic bronchoscopy for CAO (12). Technical success was achieved on average in 93% of cases which was defined as opening of >50% of the airway. Dyspnea and QOL were measured using the Borg score and SF-6D in a portion of the study patients (187 and 183 respectively) with dyspnea subjectively improved in 48% of cases and QOL improved in 42%. Greater dyspnea at baseline as well as endobronchial obstruction was associated with greater improvement in dyspnea and QOL. American Society of Anesthesia (ASA) scores >3, renal failure, lobar obstruction, and tracheoesophageal fistulas were associated with less improvement.

The above trial like many of the other papers published on this topic, generally use a validated dyspnea or QOL score as the primary outcome. A recent prospective case series examined 53 patients undergoing therapeutic rigid bronchoscopy over a 3-year period and measured QOL and dyspnea scores as well as changes in pulmonary function testing (13). The population examined was predominantly malignant (45%) and post-transplant stenosis (43%) related CAO. Patients were found to have a subjective improvement of dyspnea and QOL measured by the University of San Diego Shortness of Breath Questionnaire and the SF-36 respectively, both validated tools to assess dyspnea and QOL in lung disease patients. Besides subjective improvements this study also showed a statistically significant improvement in FEV_1 as well as FVC. There has yet to be any data showing improvement in survival after relief of malignant CAO.

Rigid bronchoscopy

Equipment

The rigid bronchoscope is a simple piece of equipment that has not significantly changed since its invention. Rigid bronchoscopes generally come in two forms; rigid tracheal scopes and rigid bronchoscopes. Both are hollow metal tubes with beveled distal edges available in several different diameters. The rigid bronchoscope is longer allowing access into the right and left bronchial trees as well as having distal fenestrations to allow ventilation of the contralateral bronchial tree. All scopes come with a built in or attachable port for jet or conventional ventilation. The light source can either be attached to the barrel, or more commonly directly to the camera. Scopes come in various sizes and length depending on the manufacturer, but all have an inner

Figure 1 Three categories of central airway obstruction (CAO). (A) Intrinsic CAO: patient with mucoepidermoid carcinoma; (B) extrinsic CAO: patient with metastatic osteosarcoma with compression of RMSB; (C) combined intrinsic and extrinsic CAO. Patient with compression of the bronchus intermedius by a right sided primary lung malignancy as well as endobronchial tumor. RMSB, right main stem bronchus.

and outer diameter varying from 7-13 mm and 8-14 mm respectively.

Although there have not been significant advances in the rigid bronchoscope itself, countless types of instruments have been developed to use through the working channel. The first and most commonly used being the flexible bronchoscope. Once the airway has been secured with the rigid scope a flexible scope is often passed through the working channel and into segmental airways to lavage, suction secretions or blood as well as cannulate past smaller obstructions prior to coring, excising or stenting. A multitude of other instruments are now also available to pass down the working channel of rigid scopes including rigid and flexible suction catheters, different types and sizes of forceps, scissors, rigid and balloon dilators, multiple types of lasers, electrocautery, argon plasma coagulation and cryotherapy catheters, snares, loops, baskets, microdebriders, and stent deployment devices (14). Finally, a manual or automated jet ventilator is needed for oxygenation and ventilation during cases. If preferred or necessary the patient can also be ventilated by packing the mouth, placing silicone caps on the end of the rigid bronchoscope and using conventional positive pressure ventilation through a ventilator circuit adaptor placed on the proximal end of the rigid scope.

Rigid intubation and anesthetic considerations

Prior to rigid intubation the operator must discuss induction with the anesthesiologist, including medication choice and paralysis as well as a backup plan incase

difficulty is encountered with rigid intubation. They must also ensure all equipment is ready and functional as well as properly position the patient to optimize first attempt success. Rigid bronchoscopy requires careful planning, cooperation and communication between the operator and the anesthesiologist to ensure patient safety.

Choice of induction agent is generally left to the anesthetist, depending on the patient's medical history and clinical stability. Rigid intubation, similar to endotracheal intubation is extremely stimulating and generally deep sedation is required to blunt the gag reflex. Total intravenous anesthesia (TIVA) is almost exclusively used for rigid bronchoscopy, as a fully closed system required for inhaled anesthetics is rare. Generally a combination of a hypnotic administered simultaneously with a narcotic is used with the most common drugs being propofol (40-200 µg/kg/min) and remifentanil (0.05-0.5 µg/kg/min) (15). Similar to endotracheal intubation paralysis is not required during rigid intubation but can be helpful especially in patients with anterior or difficult airways. If paralysis is going to be administered the choice of agent should be discussed with the operator. When a short case is expected a shorter acting agent such as succinylcholine should be considered as a one-time dose or as an infusion. Otherwise, longer acting agents such as cisatracurium, vecuronium or rocuronium can be administered (15).

Once a plan for induction has been established and all equipment is ready the patient should be positioned with a shoulder roll or the head of the bed dropped to allow maximal extension of the neck without allowing the head to float. A tooth guard should be placed to protect the

upper teeth, however if proper technique is used minimal to no pressure should be placed on the patient's teeth. The operator should then scissor the patient's mouth open in standard technique and carefully insert the rigid scope initially visualizing the tongue and hard palate. The operator's thumb should be used to support the bottom of the rigid scope just outside of the oral cavity with the index and possibly the middle finger placed in the patient's mouth resting on the hard palate. The scope is carefully inserted into the mouth with the bevel up or towards the tongue. The scope should then be carefully advanced further into the oral cavity until the uvula is visualized. Once the uvula is visualized the dominant hand holding the rigid scope and camera should be lowered using the thumb as a fulcrum and advanced further until the epiglottis is seen. The bevel of the rigid scope should then be used in a similar fashion as a Miller laryngoscope to lift the epiglottis anteriorly exposing the arytenoids, vocal cords and the glottis. If the patient's glottis is anterior the thumb should be used to apply anterior and upward force on the rigid scope to expose the glottis. Care should be taken not to use the patient's teeth as a fulcrum as this can cause significant damage. Once a good view of the glottis is achieved the scope is then rotated 90 degrees to allow the bevel to pass a traumatically through the vocal cords. The scope is then rotated another 90 degrees with the bevel rested on the posterior membrane of the trachea (16).

Once intubation is complete the jet ventilator is attached or the mouth is packed and ventilation is initiated and ensured by watching for chest rise prior to the initiation of any diagnostic or therapeutic interventions. The patient is monitored using continuous pulse oximetry, EKG tracing and blood pressure monitoring. Placement of an arterial line for blood pressure and blood gas analysis is generally not required unless the patient is unstable or a longer case is expected.

Ventilation techniques

Once rigid intubation is complete and the patient's airway has been secured the operator must turn their attention to ensuring adequate oxygenation and ventilation. These are achieved with either jet ventilation or less commonly through conventional positive pressure ventilation. Sanders originally described open system manual jet ventilation in 1967, a technique still currently in use (17). The jet ventilator is connected to a 100% oxygen source and has a pressure-limiting device peaking at 50 PSI or less. The jet is connected through a catheter to the ventilation port of the rigid scope being used. Breaths are delivered to the patient at a rate of 12-18 per minute with the breath length and expiratory time being controlled by the anesthesiologist who is monitoring chest rise and vital signs to ensure adequate ventilation. The tidal volume of delivered air is dependent on the length of the breath given, the inspiratory pressure (PSI), the compliance of the patient's respiratory system and the resistance of the patient's airways (18). The advantage of jet ventilation is the ability to keep the working channel of the rigid bronchoscope completely open allowing easy passage of instruments. Disadvantages include the ability to only use 100% oxygen (unless an ambient air blender is available) as well as difficulty in oxygenating and ventilating sicker patients with severe parenchymal or obstructive lung disease.

A second type of jet ventilation commercially available is the automated jet ventilator. This is a computerized ventilator where the operator or anesthesiologist is able to set the applied pressure, respiratory rate, FiO_2 and inspiratory time. The advantages of an automated system is the ability to free the anesthesiologist from holding the manual jet throughout the case as well as the ability to vary the FiO_2 to enable the use of thermal ablative techniques without completely holding ventilation.

Closed system ventilation is achieved by attaching a ventilator circuit adaptor onto the distal end of the bronchoscope and using the rigid scope as an endotracheal tube. All of the proximal ports of the scope must be covered with silicone caps and the patient's mouth must be packed with gauze to ensure minimal air leak. The advantage of this system is the ability to give positive pressure breaths through an automated ventilator circuit as well as positive end expiratory pressure (PEEP). This may allow improved ventilation and oxygenation in sicker patients with less respiratory reserve. A closed system also allows the use of inhaled anesthetics without significant exposure to those in the operating room. The disadvantages are the labor-intensive nature of packing the mouth as well as covering the proximal ports of the rigid scope with silicone caps, which can make the passage of multiple instruments difficult.

Tumor excision, coring and airway dilation techniques

After the patient has been successfully intubated with the rigid scope and ventilation has been initiated attention can be turned to relieving the CAO. Several different

techniques can be utilized at this time and depends on the category of CAO encountered; extrinsic, intrinsic or mixed. For pure extrinsic compression without any mucosal or endobronchial involvement therapeutic intervention relies on CRE balloon and rigid dilation followed by silicone or covered metal stent placement to maintain a patent airway.

In the setting of intrinsic or mixed obstructions the initial goal is to establish patency of the airway. It is of critical importance that the operator maintains good visualization of the airway as well as appropriate spatial orientation to avoid perforation of the airway and invasion into the surrounding mediastinal structures. Once the operator has established good visualization, appropriate spatial orientation and a parallel axis to the central airway a decision can be made on how to remove the obstructing lesion. The first option is coring with the rigid scope, this allows one rotary forward motion to remove the lesion from the wall and simultaneously allows the scope to provide hemostasis at the site. Ensuring spatial and parallel axial orientation is of utmost importance during this method as one can easily core through an airway into the mediastinum (16). The next option includes mechanical excision with optical cup forceps, free forceps, loop cautery, microdebrider or a cryoprobe.

Microdebriders are powered instruments that consist of a hollow shaft with a rapidly rotating blade and suction. This device has been used for many years by the otolaryngology community for sinus and tracheal surgery (19). More recently, the procedure has been used as an alternative to or in conjunction with other modalities such as laser excision or electrocautery. Airway debulking with the microdebrider is accomplished by shaving and suctioning tissue under direct telescopic guidance through the rigid bronchoscope.

In a study by Lunn and colleagues, 16 subjects were treated with the microdebrider for the management of CAO. The majority of patients (87%) suffered from benign airway disease and remaining three patients (13%) had malignant airway obstruction. Using the microdebrider, the obstructing airway lesions were rapidly removed in all patients. There was only mild bleeding that occurred and was easily controlled by utilizing the rigid bronchoscope to tamponade the affected area or instillation of oxymetazoline hydrochloride. In this study, there were no procedure-related or long term complications of the microdebrider reported (20). A case report by Kennedy and colleagues reports the safe use of the microdebrider for more distal lesions due to the devices long length. The microdebrider was successfully used for relief of a distal left mainstem

obstruction in a 59-year-old male with T3N2M1 non-small cell lung cancer followed by stent placement (21).

The oscillatory speed of the device and level of suctioning have varying adjustment levels and there have been reports in the literature of inadvertent resection of normal tissue with aggressive suctioning. There is one case report in the literature of pneumomediastinum and retroperitoneal air after the removal of tracheal papillomas with the microdebrider and jet ventilation. The author's hypothesize those micro-perforations occurred within the tracheal wall in conjunction with jet ventilation and allowed air entry into the mediastinum and retroperitoneum. In this case, spontaneous resolution ensued without the need for surgical or medical intervention (22).

The microdebrider requires a rigid bronchoscope or laryngoscope and due to its rigid structure is not amenable to the flexible bronchoscopic technique. The advantages of the microdebrider for management of CAO include the ability to rapidly destroy and excise tissue with minimal bleeding, the ability to maintain a clear working field due to the automatic suctioning of the debrided tissue and no risk of airway fire or perforation. Although the technology appears promising and a useful modality in the management of CAO, further studies are required to assess the long-term outcomes of the microdebrider compared with more conventional therapy (14).

Cryotherapy is another safe and effective tool for debridement, hemostasis and removal of clot in rigid bronchoscopy. The device releases nitrous oxide or carbon dioxide stored under pressure into the tip of the cryoprobe which rapidly cools to −89 ℃. The effectiveness of cryotherapy depends on the rapidity of the freezing and thawing process, the lowest temperature achieved the number of freeze-thaw cycles, and the water content of the tissue (23). Compared to other techniques for tumor destruction, the effects of cryotherapy are delayed, and frequently a repeat bronchoscopy to remove the necrotic tissue is required (24).

Cryotherapy has been used to successfully treat both benign and malignant CAO. It is effective in reducing or eliminating hemoptysis due to malignant disease in up to 93% of patients (25), and Maiwand and Homasson recommend cryotherapy as a first-line treatment in patients with post-transplant anastomotic strictures (26). As cartilage and fibrous tissue are relatively cryo-resistant, cryotherapy remains a very safe procedure. Bleeding is also uncommon because of the hemostatic effects of cryotherapy. Because of the lack of electrical current needed, cryotherapy is not

associated with the risk of airway fires, electrical accidents, or radiation exposure. Cryotherapy can be used via both the rigid and flexible bronchoscopes. When using the flexible bronchoscope, care must be taken to have the probe protrude outside the distal tip of the scope, so as not to freeze the video chip.

After relief of the CAO due to an intrinsic or mixed lesion the operator must decide whether to leave the airway as is or if a stent is needed to maintain patency and stabilization. The risk of stent migration, granulation tissue formation and mucostasis must be weighed with the benefit of continued patency provided by the stent. This will be discussed extensively in the following section.

Silicone stenting

Introduction

Dr. William Montgomery is credited with initiating the widespread use of airway stents after his development of a silicone T-tube in 1965, but it wasn't until 1990 that Dumon introduced that first completely endoluminal airway stent. The endobronchial stent remains the only tool available to alleviate extrinsic airway compression, but can be used in conjunction with other therapies to relieve CAO in those with intrinsic or mixed disease.

There are two main types of endobronchial stents available for use in the United States; silicone and metal. Silicone stents have been in use since the 1960's and have a long track record of safety. Metal stents continue to evolve from the original uncovered metal stents to a number of newly designed covered metal stents made of nitinol. Unfortunately, the "ideal stent" has not yet been developed. This stent would be easy to insert and remove, yet not migrate; of sufficient strength to support the airway, yet be flexible enough to mimic normal airway physiology and promote secretion clearance; biologically inert to minimize the formation of granulation tissue; and available in a variety of sizes.

Types of silicone stents

Most of the commercially available silicone stents are based on the original Dumon stent, which is a silicone tube with external studs to decrease migration. The Dumon silicone stent comes in two main types' straight and Y. Both types of these stents come in various lengths, diameters and shapes. The shape can be a uniform diameter throughout the length of the stent or have an hourglass shape with a narrow central portion allowing optimal positioning around a stenotic airway. Silicone stents can also have one end with a smaller diameter for optimal positioning. Y stents come with multiple various tracheal and bronchial limb diameters. These stents generally come in a uniform length, which can be adjusted at that time of insertion by shortening each of the three limbs to the desired length using a scalpel during the procedure. Other modifications can also be made at the time of insertion including the cutting of holes to allow ventilation of lobar bronchi covered by the stent during placement. Silicone stents can be made of transparent non-radio opaque material, or melted with barium sulfate, which are white in color, non-transparent but radio-opaque (27).

Another type of silicone stent commercially available currently is the Polyflex silicone stent (Boston Scientific, Natick, MA, USA). This stent is made of polyethylene threads embedded in a layer of silicone. These stents have a thin wall resulting in a better inner to outer diameter ratio compared to a Dumon stent. However, as they are not studded on the outside may have a higher rate of migration. They are embedded with tungsten making them radio-opaque and are deployed out of a semi-rigid tube inserted down a rigid bronchoscope. There are a small number of other companies commercially producing other types of silicone stents such as those manufactured by Hood (Hood Laboratories, Pembroke, MA, USA) with similar properties as the Dumon stent.

Dynamic Y tracheobronchial airway stents are also commercially available. These were initially described by Freitag *et al.* in 1994 (28) and are composed of anteriorly placed U shaped metal rings in the tracheal limb, with a silicone posterior membrane that can be dynamically compressed during cough to physiologically mimic the human trachea and allow for better mucus clearance. Finally, there are also numerous types of T-tubes and T-tube Y stent combinations manufactured currently for different types of tracheal and carinal pathology. This review will primarily focus on endobronchial silicone stents (27).

Indications

There are several indications for the use of silicone stents in the management of CAO. In general silicone stenting is indicated for maintaining central airway patency due to malignant and non-malignant disease causing greater than 50% stenosis of the trachea or bronchi. The first major indication includes stabilization of airways from malignant

CAO. This can be either due to extrinsic compression, endobronchial tumor or a combination as described above. Stents may be the only resource available to maintain airway patency in extrinsic compression, as simple dilation is extremely transient if successful at all. In terms of endobronchial disease and mixed obstruction, stents are generally placed after excision and destruction of tumor has occurred to maintain patency and attempt to avoid recurrent obstruction by tumor re-growth or until systemic chemotherapy or radiation treatment has time to take effect. Post obstructive pneumonia caused by malignant airway obstruction is another appropriate indication, which may be necessary to maintain patency and provide adequate source control of the infected lobe or segment (29).

The second major indication is treatment of benign CAO caused by intubation trauma, tracheostomy, connective tissue disease, cartilaginous disorders or benign adenopathy. Silicone stents play an even larger role in benign disease, as they are preferred over metal stents due to complications with granulation of metal stents into the airway, difficulty with removal and fistula formation. Another benign indication for silicone stenting is stabilization of collapsing airways secondary to tracheobronchial malacia or cartilaginous disorders such as relapsing polychondritis. Finally, the last category of disease necessitating silicone stenting is to cover airway-esophageal or airway-mediastinal fistulas caused by malignant disease, iatrogenic complications of esophageal stenting, radiation therapy, or dehiscence of transplanted airways (29).

Deployment

Once a lesion has been dilated, excised or destroyed and the decision has been made to place a silicone stent several steps must be taken to ensure the appropriate stent is placed in a safe, accurate and timely manner. Deployment is still based on the original technique describe by Jean Francois Dumon in a 1990 paper published in Chest of 118 stents placed in 66 patients in Marseille, France (30).

The initial step prior to deployment is choosing the appropriate size and length of the stent to be placed. This is extremely important as proper sizing decreases the chance of migration (under-sizing) and the formation of granulation tissue, airway fistulization or difficulty in deployment (over-sizing). The length and diameter of a stent can be estimated using a chest CT prior to the procedure, but measurements during bronchoscopy are the only accurate way of sizing a stent. The diameter can usually be determined by choosing

a size similar to the largest external diameter of the rigid bronchoscope used to maximally dilate the lesion in question. There are also commercially available stent sizers that can be placed down a rigid scope and used to measure the diameter of the stenotic airway. Once an appropriate size has been determined the length of the lesion should be measured using the rigid camera or flexible bronchoscope with the stent extending about 5-10 mm proximal and distal to the lesion. In sizing stents for fistulas, one should slightly oversize the stent as there is no endobronchial lesion to anchor the stent to, making migration more likely (27).

Once the appropriate stent has been selected it is loaded into a hollow metal stent deployment tube either manually or with a commercially available loading device. The rigid bronchoscope should then be placed slightly distal or within the stenosis. A prosthesis pusher is then placed through the hollow stent deployment tube and these are both placed down the rigid bronchoscope as ventilation is held. If the scope is positioned distal to the lesion, the rigid scope can be slightly withdrawn simultaneously as the stent is deployed to allow the stent to deploy within the stenosis. The deployment device is then removed and the camera alongside forceps should be placed back into the rigid scope. The stent may fully deploy, but generally requires being pulled back into optimal position, or slightly rotated to fully open. If manual rotation or adjustment does not fully open the stent the barrel of the rigid scope can be used to open the stent carefully without pushing it distally or a CRE balloon may be used to help expand the stent (30). If that is still unsuccessful, the stent is likely too large for the lesion and needs to be removed with a smaller diameter stent re-deployed.

Deployment of a Y silicone stent is slightly more difficult and can be accomplished through two general strategies. In both techniques the stent is loaded into the stent deployment device after lubrication with care taken to note the directionality in which the stent is folded in order to deploy the left and right limbs in the proper orientation. In the first technique the rigid bronchoscope is positioned above the carina based on the length of the tracheal limb. The stent is pushed out into the trachea in a similar fashion as described above and then using a camera, forceps and the rigid scope the stent is advanced and turned to position the left and right limbs appropriately in their respective mainstem bronchi flush with the carina.

In the second technique the stent is loaded in the same manner but deployed in the mainstem that will house the

longer limb of the Y stent or alternatively the mainstem with the more stenotic airway. In this technique a rigid bronchoscope must be used and intubation of the right or left mainstem must be possible. Once the mainstem has been intubated the stent deployment device is inserted into the bronchoscope and the stent is pushed out of the device. As the stent is being deployed the rigid scope is slowly withdrawn back into the trachea until the stent is fully out of the deployer. The rigid telescopes as well as forceps are then used to pull the stent back gently from the mainstem it was deployed in, allowing the shorter limb to fall into place in the contralateral bronchus. Again rotation of the stent may be necessary to allow snug seating on the carina.

Deployment of a dynamic Y stent described in the previous section must be done in an altogether different manner than the two techniques described above. After inspection of the airway with a rigid or flexible bronchoscope and measurements made to determine the size of the dynamic Y stent to be placed the scope is removed and the patient ventilated with a bag valve mask or laryngeal mask airway until the stent is ready to be deployed. The dynamic Y airway stent is loaded onto a specific deployment device, which is a modification of rigid foreign body retrieval forceps, with longer jaws onto which the right and left mainstem limbs are inserted over. The operator then using direct laryngoscopy with either a Macintosh or Miller blade inserts the stent at a 90 degree angle carefully through the vocal cords on top of the deployment forceps using their right hand. Once the stent is fully inside the trachea, the stent is rotated 90 degrees clockwise and advanced until slight resistance is met. At this point the jaws of the forceps are opened and the stent is pushed further forward onto the carina (using a device connected to the deployment apparatus) until further resistance is met. At this point the jaws are closed and the deployment forceps withdrawn from the glottis. The patient is then rigidly intubated and the rigid camera and forceps are used to adjust the stent if necessary by further pushing it forward or rotating it to optimally seat it on the carina. The patient does need to tolerate a certain amount of apnea during deployment of a dynamic Y stent and the operator must be confident in their ability to obtain a good glottic view and rapidly re-intubate the patient with the rigid bronchoscope in the case of poor deployment and obstruction of the trachea by the stent. To aid in intubation or for training purposes, placement of dynamic Y stents with a video laryngoscope can be done to allow both the trainee and instructor to have a view of the glottis (31).

Complications

There are a wide range of complications related to rigid bronchoscopy and placement of silicone tracheal and bronchial stents ranging from as minor as mucostasis to death from hypoxic arrest during placement or migration of the stent. Complications from rigid bronchoscopy and stenting are in general very low, however when consenting a patient prior to a procedure a multitude of risks should generally be discussed including trauma to the oral cavity (lips, gums, teeth, tongue, pharynx), the vocal cords, the trachea and bronchi themselves, bleeding, infection, tracheal or bronchial rupture, hypoxia, respiratory failure requiring mechanical ventilation, tracheostomy, cardiac arrest and even death. If stenting is to be performed then the risks of stent placement are generally listed including mucus plugging, migration, formation of granulation tissue, bacterial overgrowth, halitosis and repeat procedures to inspect the stent, adjust if migrated and remove granulation tissue. Depending on the clinical stability of the patient different levels of emphasis can be placed on more serious complications such as respiratory failure and death. The overall risk and benefit of the procedure can then be discussed with the patient and family and an informed decision can be made to proceed, even in high-risk situations.

Most studies examining complications following bronchoscopic treatment of CAO have been retrospective in nature, however a recent multicenter registry trial published by Ost *et al.* examines 1,115 procedures performed on 947 patients at 15 centers from 2009 to 2013 (32). These included flexible (34%) and rigid (66%) therapeutic bronchoscopy under both general anesthesia (86%) and moderate sedation (14%) with multiple interventions reported including dilation (40%), ablative technologies: cryotherapy (8%), APC (35%), laser (23%) or electrocautery (21%) and stenting (36%). Only 44 patients (3.9%) were reported to have complications, which were defined as: bleeding requiring intervention, pneumothorax, hypoxemia, clinically significant airway injury, hypotension, arrhythmia, cardiac arrest, respiratory failure requiring mechanical ventilation and death. Of those reported complications 61% of those patients required a higher level of care. There were six deaths reported within 24 hours, four of which were secondary to a complication of the procedure and two unrelated. Two more deaths >24 hours after the procedure, but thought to be secondary to a complication of the procedure, were also reported. This gives a total mortality rate of 0.5% due to

complications from therapeutic bronchoscopy.

Risk factors for complications included emergent procedures, ASA >3, re-do therapeutic bronchoscopy and the use of moderate sedation. Of note the use of neuromuscular blockade was associated with decreased rate of complications. This is likely due to the ability to oxygenate/ventilate better during the procedure as well as improved visualization due to lack of cough and patient movement. The study also examined risk factors for death at 30 days (14.8%) which were found to be associated with ASA >3, intrinsic or mixed obstructions or placement of a stent. The association with stenting and higher 30-day mortality is not likely due to the stent itself or stent complications, but rather to confounding factors including the fact that patients requiring stents likely have a higher level of disease burden are generally sicker and may not have other systemic treatment options remaining. Overall, the mortality/morbidity from therapeutic bronchoscopy is low when used in the appropriate setting.

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Footnote

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The role of bronchoscopy in the diagnosis of airway disease

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Abstract: Endoscopy of the airway is a valuable tool for the evaluation and management of airway disease. It can be used to evaluate many different bronchopulmonary diseases including airway foreign bodies, tumors, infectious and inflammatory conditions, airway stenosis, and bronchopulmonary hemorrhage. Traditionally, options for evaluation were limited to flexible and rigid bronchoscopy. Recently, more sophisticated technology has led to the development of endobronchial ultrasound (EBUS) and electromagnetic navigational bronchoscopy (ENB). These technological advances, combined with increasing provider experience have resulted in a higher diagnostic yield with endoscopic biopsies. This review will focus on the role of bronchoscopy, including EBUS, ENB, and rigid bronchoscopy in the diagnosis of bronchopulmonary diseases. In addition, it will cover the anesthetic considerations, equipment, diagnostic yield, and potential complications.

Keywords: Bronchoscopy; lung disease; diagnosis; endosonography; electromagnetic fields

Introduction

Bronchoscopy has come a long way since it was first described in 1897 by Gustav Killian, who had used it to remove a pork bone from a farmer's airway (1,2). Since that time, bronchoscopy has evolved to become an integral tool for thoracic surgeons both for evaluating airway and lung pathology and for therapeutic interventions. The modern rigid bronchoscope was first described by Philadelphia based otolaryngologist Chevalier Jackson in 1904 (3). Although it is currently used primarily for therapeutic interventions, it is still a valuable diagnostic instrument and a skill that physicians should be familiar with. Flexible bronchoscopy was first used in 1967 and with technological advancement the development of endobronchial ultrasound (EBUS) and electromagnetic navigational bronchoscopy (ENB) have provided endoscopic tools to examine and biopsy mediastinal and peripheral pulmonary lesions (PPL) (1).

This review will focus on the role of bronchoscopy, including EBUS, ENB, and rigid bronchoscopy (RB), in the diagnosis of bronchopulmonary diseases. In addition, it will cover the anesthetic considerations, equipment, diagnostic yield, and potential complications.

Anesthetic considerations for bronchoscopy

Maintaining the airway is critically important while performing a procedure that instruments the airway passages for direct viewing or interventional procedure. If there are separate anesthetic provider and proceduralists, there is significant co-management of the airway, and therefore close communication is critical. During induction, the bronchoscopist should be present and ready to establish emergency airway access as induction of anesthesia may lead to loss of a previously patent airway (4). If this were to occur, RB or a surgical airway access should be performed

if standard measures to establish endotracheal intubation are unsuccessful. This will be particularly important in cases involving airway foreign bodies and mediastinal masses. Aside from these considerations, anesthetic management for flexible bronchoscopy and RB can vary significantly.

Flexible bronchoscopy can be performed under sedation or general anesthesia. Relative contraindications to sedation include history of severe gastroesophageal reflux, history of aspiration, respiratory compromise, and extreme anxiety. Sedation can be accomplished in a number of ways including any combination of propofol or dexmedetomidine infusion, midazolam, and fentanyl. Ketamine is less commonly used due to its propensity to increase airway secretions and cause hallucinations (5). Topical anesthesia is useful as well with lidocaine being the anesthetic of choice (6). Strategies for topical anesthesia include transtracheal injection, nebulized solutions, and topical application to the posterior pharynx either by having the patient gargle viscous lidocaine or by direct spray to the mucosa of the larynx and trachea (5-7). If general anesthesia with an endotracheal tube (ETT) is required, a large ETT is ideal as the presence of the flexible bronchoscope in the ETT significantly reduces airway diameter and increases airway resistance. For an adult flexible bronchoscope, the minimum size ETT should be 8.0 mm internal diameter. Using a smaller ETT may lead to intrinsic PEEP and dynamic hyperinflation (5-7). When not contraindicated, a laryngeal mask airway (LMA) should be considered as it has a larger diameter conduit for the flexible bronchoscope thus reducing airway pressures. In addition, it allows for complete visualization of the trachea from the vocal cords whereas the ETT has to be extracted to view the proximal trachea and vocal cords (6).

Rigid bronchoscopy requires general anesthesia and almost always paralysis. A total intravenous anesthetic (TIVA) with propofol is the most common technique for maintenance of anesthesia. Remifentanil is an ideal adjunct for a TIVA as it tends to provide dense, short acting, and predictable analgesia (6,7). Short acting, non-depolarizing agents or a succinylcholine drip are preferred (5,7). Many different ventilatory strategies have been successfully used. The simplest technique is to use the standard semi-closed circuit by connecting the ventilator circuit to the side port of the rigid bronchoscope, essentially treating the bronchoscope like an ETT. Ventilation is held whenever the eyepiece is removed from the proximal end for suction or biopsy. Additionally, if a telescope is passed through the rigid scope, ventilation through the side piece via the standard ventilator circuit will not be possible. While an

inhaled agent can be used with this system, delivery may be hampered by frequent pauses in ventilation and due to suctioning. Additionally, high flows (up to 20 L/min) may be required to compensate for leaks in the system, which leads to inefficient delivery of the inhaled anesthetic and leakage of gas into the operating room (4,7,8). Saline soaked gauze can be packed in the posterior oropharynx to help reduce the leak. A Jackson-Reese circuit can also be connected to the side port of the rigid bronchoscope with intermittent volume ventilation performed by squeezing the bag whenever the scope is free of a telescope. Again, the proximal end must be occluded with the eyepiece to allow for ventilation to occur. Because a large portion of the time RB is performed for intervention, and the working channel needs to be open, the authors prefer jet ventilation. Jet ventilation uses an injector bronchoscope, however, some find it undesirable as it can create noise and aerosolized secretions (4). Additionally, patients are at risk for barotrauma and hypercarbia with this technique (6,8). With jet ventilation, it is critical to keep the end of the bronchoscope open to avoid accumulation of pressure and barotrauma (9). Apneic oxygenation can be performed as well using a small catheter positioned alongside the bronchoscope to insufflate oxygen, but this technique is rarely used due to the propensity for significant hypercarbia.

Flexible bronchoscopy

Flexible bronchoscopy is simple to learn and provides many benefits as a diagnostic, but also a therapeutic treatment option for patients with bronchopulmonary diseases. Flexible bronchoscopes have a fiber-optic light source that illuminates the distal end of the scope allowing for visualization of the airways. A suction port allows for aspiration of fluid and de-fogging of the camera through a working channel. A single forward and backward toggle bends the tip of the scope 120–180 degrees, and when combined with wrist rotation allows access from the trachea to the quaternary airways.

Flexible bronchoscopes come in many different variations, but generally there are three size categories: pediatric, adult, and therapeutic scopes. Pediatric or ultrathin scopes have an outer diameter of 2.8 mm and working channel width of 1.2 mm. The smaller channel size allows for the passage of small instruments such as cytology brushing and biopsy forceps, as well as, for suctioning and bronchoalveolar lavage (BAL) collection. Pediatric scopes have a more narrow scope body that can allow for

navigation around obstructing lesions; however, the image clarity is often limited in scopes of smaller sizes.

The larger typical adult scopes have an outer diameter of 4.9–5.5 mm and a working channel size of 2.0 mm. This size working port allows for biopsy forceps or needles, baskets, and greater suctioning abilities, as well as, some other diagnostic and therapeutic adjuvants. Therapeutic bronchoscopes have the largest working channel width (2.8–3.2 mm) and outer diameter of 6.0–6.2 mm. The larger working channel (>3 mm) is needed for laser or electrocautery device insertion.

Older generation fiber-optic bronchoscopes have an eye piece, but most institutions use video-linked bronchoscopes that display the images on video monitors which allow for improved teaching platforms and visualization for multiple operators while performing complex interventions.

The bronchoscopy procedure is very well tolerated and most commonly performed as an outpatient day procedure. Adverse events are rare but include: bleeding (0.12%), hypoxia, loss of airway, pneumothorax (0.1–0.16%), or mortality (0–0.02%) (10-12).

The most common uses for flexible bronchoscopy include: diagnosing potential airway injury or obstructions such as with foreign body or tumor, biopsy of airway masses for diagnosis, specific guided endobronchial washings for diagnosis of micro-bacterial evaluation, or pulmonary hygiene for pulmonary lobar collapse. Visual inspection of the airway is the simplest diagnostic utility with flexible bronchoscopy. The airway is evaluated for possible intraluminal irregularity, obstruction, foreign body, fluids and mucous, inhalation injury, caustic ingestion, or trauma.

Airway injuries may not be identified on imaging such as chest radiograph or CT scan. Liberal use of bronchoscopy in blunt or penetrating trauma aids in the diagnosis of occult airway injuries, which is important because patient outcomes were improved with early diagnosis (13,14). Inhalation burn injury leads to hyperemia in the airways of burn patients that can be visualized on flexible bronchoscopy. Bronchoscopic diagnosis of airway injury is associated with increased mortality after inhalation injuries and therefore prompt diagnosis and management is extremely important (15).

Characteristic chest X-ray findings of airway obstruction include opacification of the lung parenchyma and tracheal deviation towards the side of collapse. However, often times it is difficult to distinguish lobar collapse from a large pulmonary effusion. Flexible bronchoscopy is an excellent diagnostic tool as well as a potentially therapeutic technique

to clear mucous plugging causing lobar collapse. The procedure requires a standard (adult) size bronchoscope to fully suction thick secretions. Sterile saline is flushed through the working port in order to break up thick secretions. Culture samples should be sent in order to appropriately treat bacterial pneumonia. Bronchoscopy washings will allow for investigation of infectious pulmonary disease by obtaining culture material in order to better treat patients with targeted antimicrobials. Blind catheter aspiration should be obtained first for ventilated patient with suspected ventilator associated pneumonia, but if non-diagnostic then bronchoscopy with BAL should be considered for diagnosis (10).

Masses within the tracheobronchial tree can also lead to airway obstruction and lobar parenchymal collapse. Suspected mass evaluation via flexible bronchoscopy allows for differentiation between tumors and aspirated foreign bodies. It may also obviate the need for RB, if the foreign body can be retrieved via forceps, basket, suction, snare, or cryotherapy (16,17). Tumors are evaluated for extent of involvement by visual inspection and should be biopsied for pathologic diagnosis. For patients with suspected lung cancer, the diagnostic yield of flexible bronchoscopy alone is high (74%) when there is an endobronchial component that is visible and forceps biopsy is performed (10). The yield is increased with the addition of endoscopic brushings (18) (*Figure 1*).

Patients with airway bleeding can develop blood clots that result in bronchial obstruction. Flexible bronchoscopy can be used for evacuation of blood from the airway; however large clots often require RB for complete evacuation. Flexible bronchoscopy allows for other adjunctive treatments including cryoablation or argon plasma coagulation of bleeding lesions (19,20).

Biopsies of alveolar tissue via flexible bronchoscopy are useful in diagnosing many interstitial lung diseases including sarcoidosis, non-interstitial pneumonia, idiopathic pulmonary fibrosis, or rejection after lung transplant. Traditionally, parenchymal biopsies were obtained with flexible forceps that grasp the tissue and extract it through the working channel. However, a newer innovation cryoprobe transbronchial lung biopsy can aid in diagnosis. As the cryoprobe is activated, the tip adheres to the tissue due to crystallization of water and can thus be extracted (21).

The Wang needle was developed in 1978 and was first used to diagnose lung cancers. It was then further used to perform transbronchial biopsies of mediastinal lymph nodes. This was historically done using landmarks and
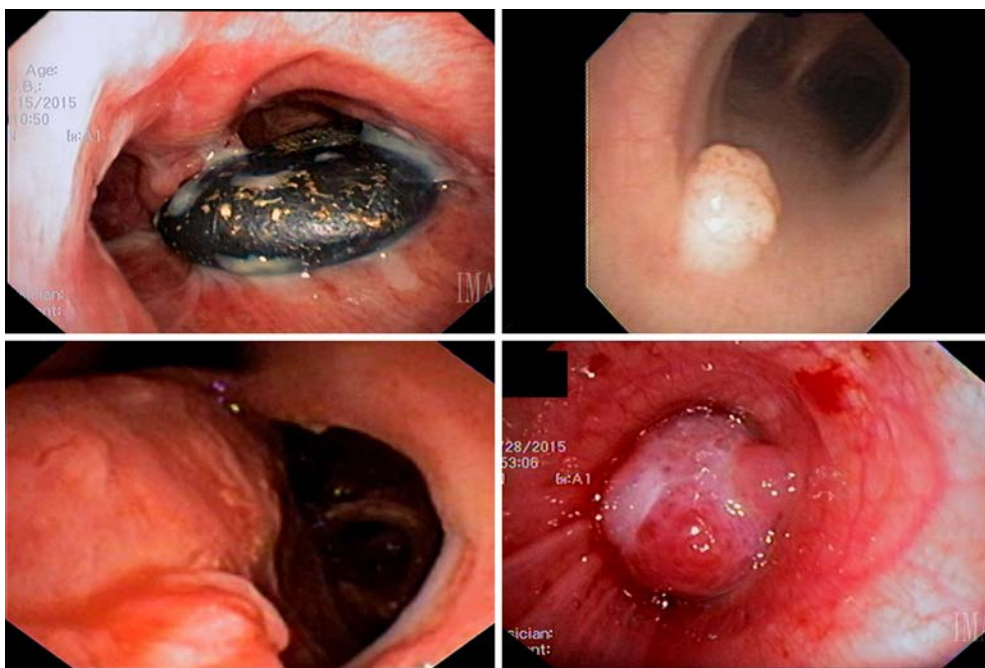
Figure 1 Examples of airway pathology identified by flexible bronchoscopy. Upper left: airway foreign body upper right: granular cell tumor of the trachea. Lower left: tracheobronchial airway injury with avulsion of the right mainstem bronchus lower right: obstructing bronchopulmonary carcinoid tumor in the left mainstem bronchus.

anatomic knowledge in a blind fashion (22). Now this is largely replaced by EBUS with biopsy as discussed below.

EBUS

The technology of EBUS has evolved significantly since its birth over a decade ago. As endoscopists gained experience with EBUS, there has been an increase in the diagnostic uses and an improved yield with biopsies. EBUS probes combine bronchoscopy with an ultrasound probe at the distal end for viewing extra bronchial structures including mediastinal vascular structures, masses, or lymph nodes. The scopes have a working channel for trans-bronchial fine needle aspiration (TBNA).

There are two main types of EBUS scopes available: radial probe and convex probe EBUS. The radial probe (UM-S320-20R, Olympus), which was developed first, does not allow for direct visualization during biopsy. It requires the probe to be placed through a guide sheath and then both are advanced through the working channel of a regular bronchoscope. After identification of the lesion of interest, the probe is removed and the working sheath remains in place and biopsy forceps or brushing wand may be inserted through the sheath for sampling (23). The convex probe

EBUS (XBF-UC260F-OL8, Olympus) is an integrated scope and transducer that allows for direct visualization during FNA biopsy (23). The balloon tipped scope allows for saline insufflation to aid in ultrasound transduction and clearer ultrasound imaging. A 21- or 22-gauge needle is inserted with sheath through the working port for TBNA while directly visualizing the biopsy target of interest. The needle extends out of the working channel into the node or lesion with the ability to apply a suction syringe to the opposing end. The needle is repeatedly passed within the tissue under direct visualization to obtain the samples. The entire needle apparatus is then removed and the tissue placed onto a slide for rapid on site evaluation (ROSE) or into a cytology container. Three to five passes of the needle is recommended for optimal diagnostic potential (24).

EBUS, like bronchoscopy, can be performed under conscious sedation with local anesthetic to the vocal cords or general anesthesia through an ETT. Complication rates are low (0–3%) and include: hypoxia, respiratory failure, pneumomediastinum, pneumothorax, cardiac complications, and bleeding. Rarely sepsis and airway injury have been reported (25-28). Lung nodules are often alternatively sampled via CT guided percutaneous biopsies, which can lead to a higher rate of pneumothorax or biopsy

tract seeding. In conventional series, CT guided biopsy has a pneumothorax rate of 15%, with 40% of these patients requiring chest tube placement (29).

EBUS-TBNA is quickly becoming the standard for diagnosis of pathologic or enlarged mediastinal lymph nodes. Needle aspiration samples are conducive to immediate pathologic evaluation and allow potential concomitant surgical resection in the appropriate settings. Lung cancer staging is the most common indication for mediastinal lymph node analysis, but EBUS is used for non-malignant pathologies as well.

EBUS evaluation of mediastinal lymph nodes for lung cancer aids in diagnosing advanced disease and allows for preoperative planning. Gold standard mediastinal sampling has traditionally been done surgically via mediastinoscopy, an invasive surgical procedure with a cervical incision. However, a recent study showed that EBUS-TBNA was more sensitive (88% *vs.* 91%) and more accurate (92% *vs.* 89%) when compared to mediastinoscopy for evaluating lymph node stations 2R, 2L, 4R, 4L, and 7 (30). The European Society of Thoracic Surgeons have thus changed their guidelines to recommend EBUS-TBNA as first line method of mediastinal lymph node assessment in patients with non-small cell lung cancers greater than 3 cm, located centrally within the lung, or with suspected N2 disease based on pre-procedure imaging (31).

Another advantage EBUS has over mediastinoscopy is the ability to sample N1 level lymph nodes (stations 10 and 11) and intrapulmonary or parenchymal lesions. Lung lesions near the airway, but not directly visualized by bronchoscopy have a diagnostic accuracy up to 94% (25). When comparing blind trans-bronchial biopsy to EBUS-TBNA, there was no difference in lesions greater than 3 cm. But with lesions smaller than 3 cm adding EBUS imaging significantly increased the trans-bronchial biopsy rate from 31% to 75% (32). Unfortunately, the sensitivity of EBUS decreases with sampling of more distal PPL. In a retrospective analysis of patients with PPL's, EBUS was found to have 60% sensitivity in establishing a lung cancer diagnosis in lesions seen on ultrasound. When including lesions not visualized, the sensitivity dropped to 49% (33). Georgiou *et al.* found similar results but also noted a higher sensitivity of 85–87% when lesions were >20 mm and an overall sensitivity of 69.7% in detecting PPL's (34). Factors that increased the diagnostic yield of EBUS for PPL's include: bronchus sign on CT, solid nodules, lesion >20 mm, and probe position within the lesion (35). A bronchus sign describes when CT imaging demonstrates a bronchus

headed directly towards the lesion of interest. Radial probe EBUS with ROSE pathologic evaluation will also increase diagnostic accuracy of PPL's (36). Endoscopic ultrasound guided FNA (through the esophagus) can increase access to left paratracheal, inferior mediastinum, and aortopulmonary window nodes. When added to EBUS-TBNA, it can increase the ability to diagnose lymphadenopathy by 7.6% (37).

Non-lung cancer pathologies investigated by EBUS include: lymphoma, sarcoidosis, or tuberculosis. In a recent retrospective analysis, the overall sensitivity and negative predictive value of EBUS-TBNA in diagnosing lymphoma were 65% and 96%, respectively (38). However, it is important to note that other studies over the last 8-year have found wide variability in the sensitivity of EBUS-TBNA for lymphoma (39-45). Most studies are limited by small sample sizes and differences in disease recurrence, as well as mixtures of patients with Hodgkins lymphoma (HL) and non-Hodgkins lymphoma (NHL). Results showed higher diagnostic sensitivity with NHL and those with recurrent disease (38).

A recent study looking at the use of EBUS-TBNA for diagnosis for sarcoidosis found an overall sensitivity of 84%. Additionally, they note that when combined with standard bronchoscopic techniques, sensitivity increases to 89%. This is compared to a sensitivity of 54% with standard bronchoscopic techniques alone (46). A systemic review and meta-analysis of EBUS-TBNA for diagnosis for sarcoidosis found an overall diagnostic accuracy of 79% (47).

EBUS-TBNA is an effective means of diagnosis of intrathoracic tuberculosis. A recent review of eight studies with 809 patients found a pooled sensitivity and specificity of 80% and 100%, respectively. This is most helpful in cases of lymphadenopathy with negative microbiologic sputum cultures (48).

As discussed earlier, flexible bronchoscopy has been used to visually inspect and evaluate malignant spread through the bronchial wall and into the lumen of the airway, which can help in clinical management and treatment options. EBUS is now being used to distinguish between compression and infiltration of the bronchial wall. Use of ultrasound to evaluate the extent of tumor involvement has previously been useful for esophageal and rectal cancer staging. Within the tracheal wall, ultrasound has an accuracy of 94% for determining tumor involvement, when compared to the resected specimens. This is much higher than CT image accuracy of 51% (49). This technology is useful for not only lung cancers, but when considering resection of thyroid or esophageal cancers with questionable
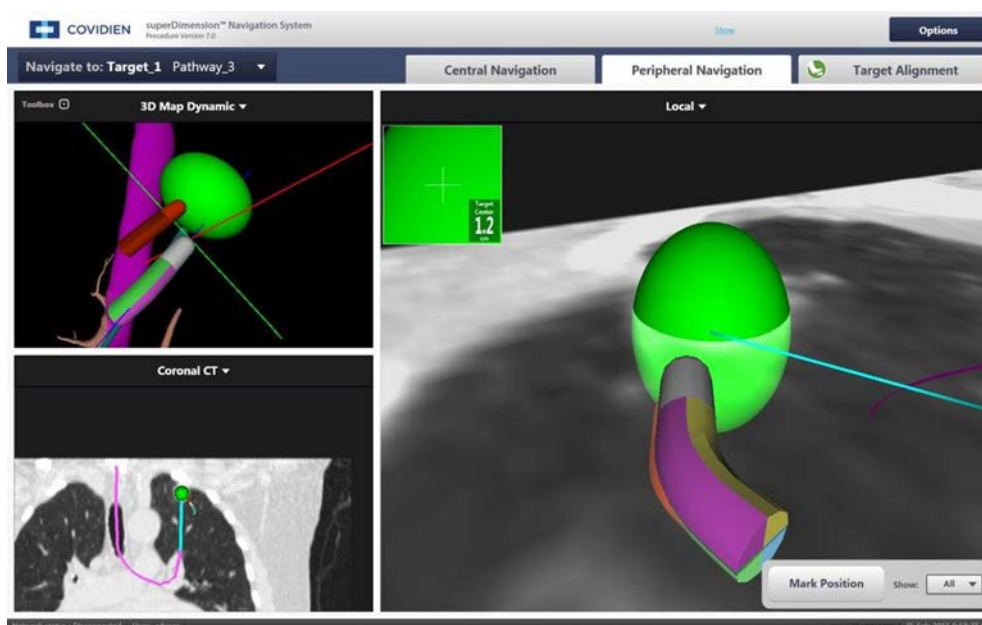
Figure 2 ENB peripheral navigation screenshot. The CT guided planned pathway is used to navigate to the left upper lobe nodule to allow for tissue sampling. ENB, electromagnetic navigational bronchoscopy.

tracheal involvement.

Navigational bronchoscopy

ENB, or more commonly called navigational bronchoscopy, became commercially available in 2006 and combines CT images with real time bronchoscopy that allows for biopsy of thoracic and pulmonary lesions. It was developed to allow for trans-bronchial biopsy of more remote peripheral lesions than those available for biopsy with traditional bronchoscopy or EBUS (50).

The technology requires iLogic virtual bronchoscopy proprietary planning software and equipment (SuperDimension™, Medtronic) (51). The system contains three components: dedicated laptop with planning software, the electromagnet mat, and a freestanding video tower. There are two phases of the procedure: the planning stage and procedure stage.

During the planning stage, a dedicated thin slice CT scan of the patient is obtained. This is then loaded into the dedicated laptop with software that identifies airways within the lung, and it renders a three-dimensional representation of the bronchial tree. A physician then must direct the computer to finalize the lesion mapping. The lesion is outlined and identified to the computer. A pathway or "road map" similar to the color-highlighted roadway maps on

conventional global positioning systems (GPS) is created that leads to the lesion. Several pathway maps to a single nodule can be stored in the computer to increase the rate of a successful diagnostic biopsy.

The patient is then taken to the procedure suite. The electromagnetic mat is placed under the patient's chest and then the bronchoscope is introduced into the airways to allow registration of the mat to the computer-generated airways based on CT scan mapping. A therapeutic bronchoscope with a 3.8-mm working channel is fitted with a steerable locatable guide that registers with the mat under the patient, which is then registered with the three dimensional reconstruction and pathways done during the planning stage (*Figure 2*). The location guide can extend out the end of the bronchoscope for biopsy out into more distal airways, reaching up to 6th to 8th generation airways (52). ENB is also used to mark peripheral lesions by injecting dye for operative identification or placement of fiducial markers for directed radiation treatment or surgical identification of a small nodule (53).

A disadvantage of this procedure is that it can only be performed after obtaining a dedicated CT scan with added radiation exposure to the patient. The additional CT scan, cost of software and a dedicated laptop computer increase the cost of this technology when compared to CT-guided biopsy (54). However, there are fewer complications than

with CT-guided biopsy including a reported pneumothorax rate of only 1% (55).

Factors which contribute to the overall diagnostic accuracy of ENB include: the presence of a bronchus sign on CT, location and size of the lesion, general anesthesia versus sedation, and the availability of pathologic ROSE (56,57). The presence of a bronchus sign significantly increases the yield of ENB biopsy compared to no discernable presence of an airway leading to the nodule (79% *vs.* 31%) (58). Not surprisingly the diagnostic yield of ENB is higher with larger nodules. When lesions are less than or greater than two centimeters, the diagnostic yield is 61% and 83%, respectively (53). However, even with smaller lesions (<15 mm) the diagnostic success rate of biopsy with ENB has been reported to be nearly 70% (59). General anesthesia was found to improve diagnostic yield slightly (69.2% *vs.* 57.5%) (57). When combined with ROSE, Karnak *et al.* found ENB to have a pooled diagnostic yield of 89.5% for both mediastinal and peripheral lesions (60).

While one of ENB's main indications is evaluation of PPL, ENB can also be used for evaluation of mediastinal lymphadenopathy. Diken *et al.* found ENB to be superior to conventional TBNA in the diagnosis of mediastinal lymphadenopathy. The overall diagnostic yield of ENB when used for diagnosis of mediastinal lymphadenopathy was 72.8% compared to 42.2% for conventional TBNA (59).

Rigid bronchoscopy

Rigid bronchoscopy is a useful tool for an interventional bronchoscopist. The instruments are not complex and have been used for numerous years. However, there are nuances that that must be learned in order for a safe procedure, therefore this procedure should only be performed by those with experience and training in RB.

Rigid bronchoscopy remains the gold standard for the management of many complex airway pathologies. The construction of a rigid bronchoscope is fairly universal consisting of a 40–45 cm straight metal tube that is open on each end. There are side holes along the distal end of the scope, which allow for intermittent ventilation. The distal end is beveled allowing for mechanical resection of obstructing lesions and facilitates opening of the vocal cords during intubation. Various diameter scopes are available including 7, 8, and 9 mm scopes for adults as well as smaller sizes for pediatric patients such as 3.5, 4, 5, and 6 mm. The largest available diameter is 13.5 mm. When choosing a scope size, one should select the largest scope that can safely pass through the glottic opening, which in a male without tight stenosis should be 8–9 mm and in a female 7–8 mm (9). The opposite end of the scope will have multiple ports that can be used for various forms of ventilation including jet ventilation, intermittent volume ventilation, or continuous volume ventilation (9,61).

Rigid bronchoscopy can be performed via direct visualization through the barrel of the scope, or via a rigid optic telescope or video scope passed down through the barrel. Alternatively, some operators will pass a flexible bronchoscope through the barrel. Illumination is accomplished via a light source attached to a light carrier running down the side of the scope or via telescope inserted in the rigid bronchoscope (62). One significant limitation to direct visualization through the barrel is the size of the field of view. The field of view will be 40–45 cm away and relatively small, making visualization of fine details difficult.

Prior to beginning the procedure, inventory of all available equipment should be taken. One should have multiple sizes of rigid bronchoscopes, large bore suction catheters, video telescopes, biopsy forceps, and rubber tooth guard or saline soaked gauze to protect the teeth readily available within the operating room suite. The planned method of ventilation should be discussed with the anesthesia provider ahead of time, as well as an alternative method. The surgeon must be present on induction of anesthesia should there be a need to establish an emergency airway.

For intubation, the patient should be placed in the sniffing position by placing the patient's head on a pillow and a roll under the shoulders. With the ventilating sidepiece of the scope upward, the scope is inserted into the mouth while protecting the teeth with a mouth piece and the provider's non-dominant thumb. The scope is directed to the base of the tongue and then elevates the tongue allowing for visualization of the epiglottis, similar to using a laryngoscope. Once the epiglottis is in view, the scope is advanced posteriorly lifting the epiglottis and exposing the glottis. Once the glottis is in view the scope should be rotated 90 degrees to allow it to traverse the vocal cords with its smaller diameter. Once past the glottis, the scope can be rotated back to its original position with the ventilating port directed upwards. To assess the right or left bronchi, the patient's head is turned to the contralateral side with the scope also placed in the contralateral side of the mouth (9).

Once intubation and visualization are achieved, the large working channel allows the variety of instruments to be used. Forceps extend down into the scope for biopsy, and large suction catheters can be used to aid in visualization

and clot removal. Additionally, endobronchial masses can be removed with the beveled end of the rigid bronchoscope by shearing tissue off of the bronchial wall. In the case of obstructing masses, the lesion can be wedged into the distal end of the scope and then the rigid bronchoscope must be withdrawn from the patient for specimen retrieval. The patient is then re-intubated with either rigid bronchoscope or standard ETT. Several passes are often required for large obstructing lesions. Jet ventilation must be held while the specimen is wedged into the end of the scope to ensure it is not expelled out the end. It is our choice to intubate with an ETT upon completion of a RB to allow for ventilation and clearing of carbon dioxide that has built up during high frequency jet ventilation. Finally, the airway is inspected with flexible bronchosocpy for complete resection, airway injury, or bleeding.

The main diagnostic indications for RB include airway foreign bodies, bleeding or hemorrhage into the airway, airway stenosis, evaluation of the airway for tracheal resection, and improved biopsy specimens when fiberoptic specimens are not adequate (9,63). Additionally, examination of the subglottic airway in the neonatal population will usually require RB, especially if any intervention is anticipated (64). RB is often used in high acuity settings, such as an airway foreign body; because once the diagnosis is established it can be used to for therapeutic intervention. Contraindications to RB include uncontrolled coagulopathy, extreme ventilatory and oxygenation demands, facial trauma, and unstable cervical spine (63).

In modern practice, RB is mostly a tool for interventions in the airway. The diagnostic value of RB has decreased with the emergence other diagnostic modalities including flexible bronchoscopy, EBUS, ENB, and high-resolution imaging. These options have become more popular due to the invasive nature of RB. Risks of RB include bronchospasm, hypoxia, and trauma to the respiratory tract including edema or bleeding. A recent review article looking at use of RB for retrieval of airway foreign bodies found that bleeding occurred in 8–17% of cases. In addition, more serious complications including pneumothorax, airway perforation, cardiac arrest, and death have been reported (65).

Rigid bronchoscopy remains the gold standard for extraction of airway foreign bodies. Righini et al suggests initial RB is indicated in cases of asphyxia secondary to obstructive foreign body, radiopaque foreign body on chest X-ray, as well as unilaterally decreased breath sounds, obstructive emphysema or atelectasis on imaging (66). Some have questioned the routine use of RB for airway foreign

bodies due to variable rates of negative studies. Various articles have quoted 7–46% negative bronchoscopy rates. Accordingly, recommendations and treatment algorithms have been suggested (65,66). In two recent studies, "obvious" cases of foreign body aspiration went directly to RB, and negative study results were still 14–18% (65,67,68). Since flexible bronchoscopy is a quick and low risk procedure, the authors advocate for a diagnostic bronchoscopy prior to RB if the diagnosis of an aspirated foreign body is in doubt.

Management of bronchopulmonary hemorrhage depends on the rate and quantity of bleeding. A therapeutic flexible bronchoscope will allow for evacuation of majority of airway blood and secretions, as well as allow for airway inspection. When there is extensive hemorrhage, the rigid bronchoscope will accommodate a large bore suction catheter to evacuate rapidly accumulating blood and remove larger formed clots allowing for visualization and identification of the bleeding source (69-71). Once the source is identified, RB affords many different modalities to quickly intervene and control bleeding (70).

RB can be used to evaluate the airway for tracheal resection. Precision is critical when evaluating whether a patient can safely undergo tracheal resection (9,72). Tracheal stenosis is most commonly evaluated by some combination of radiographic imaging and flexible bronchoscopy due to the simplicity and availability of these diagnostic modalities. In this setting, the rigid bronchoscope is used to take precise measurements of the mass or stricture and its distance to the vocal cords and carina. Rigid bronchoscopy is useful if the patient has significant tracheal narrowing in which there is risk for complete occlusion of the airway during the examination. Rigid bronchoscopy is performed with a ventilating instrumentation, which allows the operator to go past the obstruction and ventilate the patient. Furthermore, it is the procedure of choice for dilation, which is likely to be performed in this circumstance. Rigid bronchoscopy has also proven to be the most accurate in evaluating length of stenosis in the subglottic larynx. This is particularly important because specific surgical approaches are used in patients with subglottic tracheal stenosis to avoid recurrent laryngeal nerve injury. This higher accuracy is likely explained by the possibility of performing an accurate evaluation even in the patient with critical stenosis (72). Carretta *et al*. found that when used to evaluate the subglottic larynx, the sensitivity, specificity, and accuracy of RB were 67%, 100%, and 92% respectively (72).

Transbronchial lung biopsies of pulmonary lesions or diffuse parenchymal lung disease can often be obtained via

flexible bronchoscopy. Rigid bronchoscopy may be employed when biopsy specimens obtained by the tools passed through a flexible scope are not sufficient or when a large specimen is anticipated to be needed (73-75). Specimens may be crushed when being removed through the fiber-optic scope making their histological examination more challenging (75). Casoni *et al.* found that the diagnostic yield of transbronchial lung biopsies was significantly higher (78% *vs.* 65%) when using jumbo forceps via RB compared to biopsies obtained using a smaller flexible biopsy forceps (76). Others feel that RB is more widely available and cheaper when compared to more sophisticated fiber-optic techniques utilized for transbronchial needle biopsy, and suggest that RB maintains better control of the airway, have shorter procedure times, and faster control of bleeding (77).

Conclusions

Airway endoscopy is a useful tool for evaluation of airway disease and an essential skill for all physicians who manage bronchopulmonary diseases. Flexible and rigid bronchoscopy are widely available for use. EBUS and ENB have increased the diagnostic accuracy of endoscopic biopsy of mediastinal and PPL. As the focus of treatment of thoracic malignancies shift toward personalized medicine, pulmonologist and surgeons will be asked to do more endoscopic biopsies for molecular tissue testing. Given this trend, the increase in diagnostic yield, and minimal risk associated with these procedures, airway endoscopy will remain critical in the evaluation of bronchopulmonary diseases and provide safe and effective approaches to tissue sampling.

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Footnote

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The role bronchoscopy in the diagnosis of airway disease in children

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Abstract: Bronchoscopy is endoscopic examination of airways that allows both diagnostic and interventional procedures in the evaluation of airway disease in children. It can be performed with either rigid or flexible instruments, depending on the particular needs of patients and skills of bronchoscopist. In addition to visualization of airways, bronchoscopy enables to obtain specimens form lungs and distal airways. Bronchoalveolar lavage (BAL) yields samples from surfaces of the alveoli and aids differential diagnosis of various pulmonary disease. Foreign body removal and examination of anatomy and dynamics of airways are also common indications of bronchoscopy in children. Improvement in the technology, endoscopic instrumentation allows detailed evaluation and interventional manipulation of airway lesions in small children. Although bronchoscopy is considered as a safe procedure, obstruction of airway may challenge and require special endoscopic skills with appropriate instrumentation. This review is aimed to outline the role of bronchoscopy in diagnosis airway disease in children.

Keywords: Bronchoscopy; children; airway disease; rigid; bronchoalveolar lavage (BAL)

Introduction

Bronchoscopy allows direct visualization of trachea and bronchi by rigid open tube bronchoscope or flexible fiberoptic scope (1). Detailed evaluation of airways with bronchoscopy offers advantages over other diagnostic tools and allows interventional procedures such as biopsy of lesions, removal of foreign bodies, dilatations of stenosis and obtaining samples for cytological and microbiologic analysis. Bronchoscopy can be performed either by rigid (RB) or flexible (FB) instruments depending on the needs of patients. The pediatric airway is notably different from adults. It is smaller in size, larynx and tracheal proportion is more as compared to adults and epiglottis is more posterior and narrower (2). Therefore, type of bronchoscopy should be decided not only for indications but also considering the procedure specific instrumentations.

FB enables to obtain anatomical and dynamic information of airways and offers sampling from distal airways for cytological and microbiological studies (3). It is carried out under light sedation or general anesthesia. During the

procedure, patient can be spontaneously breath around a small FB and positive pressure ventilation can be needed under some circumstances. Ventilation can be also assisted via laryngeal mask, nasopharyngeal or endotracheal tube (4). Diameters of FB and endotracheal tubes are listed in *Table 1* (5). Pediatric FB are 1.8 to 4.9 mm in size with suction channels. Biopsy forceps and cytology brushes are also available for 3.5 mm and larger bronchoscopes (6). A 3.5 mm FB can be used for neonates, children and adults. It has also suction ports for bronchoalveolar lavage (BAL) but they have limited role in foreign body removal. Only small superficial tissues can be sampled with 3.5 mm bronchoscopes. A 4.7 mm FB can be used in children older than 6 years of age.

RB are performed under general anesthesia in an operating theatre setting. In children, RB can be used not only for diagnosis but also for therapeutic purposes. The main advantage of RB is that it secures the airway and allows for assisted ventilation during the procedure. RB are 3 to 7 mm in diameter and 20–50 cm in length (*Figure 1*). External diameter of RB is selected according to the weight of the child (*Table 2*) (7). Rigid telescopes such as direct

Table 1 Diameter of endotracheal tubes (ETT) and appropriate instruments

Diameter of instruments (mm)	Smallest ETT for only intubation (mm)	Smallest ETT for assisted ventilation (mm)	Smallest ETT for spontaneous ventilation (mm)
2.2	2.5	3.0	3.5
2.8	3.0	3.5	4.0
3.5	4.5	5.0	5.5
4.7	5.5	6.0	6.5
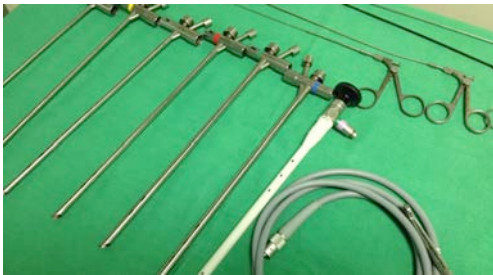
Figure 1 RB for children.

Table 2 Diameters of RB

Weight (kg)	External diameter (mm)	Internal diameter (mm)	Size number
<3	4.2	3.5	2.5
3–6	5	4.3	3
6–15	5.7	5	3.5
15–20	6.7	6	4
20–25	7.8	7.1	5
25–25	8.2	7.5	6

0° and angled (30°–70°) are available with 2.7 and 4 mm diameters.

After a brief introduction of FB and RB, it is aimed to review the role of bronchoscopy in the diagnosis of airway disease in children.

Indications of bronchoscopy

Bronchoscopy is utilized to define airway anatomy and airway dynamics, to obtain specimens for further diagnostic study. Indications of bronchoscopy are exploration of airways, obtaining biological samples and therapeutic applications (*Table 3*) (3).

Table 3 Indications of bronchoscopy

Exploration of airways
Persistent stridor
Persistent wheezing
Hemoptysis
Suspicion of foreign body
Persistent of recurrent atelectasis
Persistent of recurrent pneumonia
Localized pulmonary hyperlucency
Problems with tracheostomy or other artificial tubes
Obtaining biological samples (BAL, bronchial biopsy, brushing)
Pneumonia in immunosuppressed patients
Chronic interstitial pneumonia (hemosiderosis, eosinophilic pneumonia, etc.)
Obstruction in bronchial lumen
Aspiration to lungs
Therapeutic procedures
Aspiration of endobronchial secretions
Difficult intubations
Selective intubations
Management of foreign bodies combined with RB

Evaluating the airway anatomy and dynamics

There are several causes indicating exploration of the airways. Laryngomalacia is main cause of persistent stridor and requires FB in case of atypical presentation, biphasic character, history of difficult intubation and suffocation crisis (8). Hemoptysis is uncommon in children and mostly associated with artificial airways. Unexplained

hemoptysis requires FB to rule out endobronchial pathologies. Persistence of atelectasis more than 6 weeks with unexplained symptoms makes FB recommendable (9). If localized hyperlucency in chest X-ray is not associated with congenital or infectious causes, air trapping due to an intrinsic obstruction or extrinsic compression should be evaluated with FB. During FB, deep sedation should be avoided if air dynamics are evaluated for laryngomalacia, tracheomalacia and bronchomalacia. It is also possible to evaluate vocal cord granulomas, endotracheal or tracheostomy tube complications and laryngeal cysts (10).

Obtaining biological samples

BAL is the most common method to obtain specimen from distal airways and alveolar surfaces. It is the most important aspect of diagnostic bronchoscopy. Saline is installed into distal airways and fluid returned from the lavage is collected to measure the soluble and cellular contents alveolar surface. Since epithelial fluid is not static, it is difficult to estimate the true concentration of substances. It depends on duration and volume of the fluid employed during lavage. Therefore, specimens obtained by BAL are more useful to evaluate infectious and inflammatory process than quantitative analysis. The indications of BAL are (5):

❖ Diagnosis of suspected infection;
❖ Pulmonary infiltrates;
❖ Dyspnea;
❖ Hypoxia;
❖ Tachypnea;
❖ Recurrent and/or persistent pulmonary infiltrates;
❖ Interstitial infiltrates;
❖ Diffuse alveolar infiltration;
❖ Pulmonary hemorrhage;
❖ Alveolar proteinosis;
❖ Suspected aspiration;
❖ Lung transplant;
❖ Hypereosinophilic lung disease.

The other indication of BAL is to obtain fluid for diagnosis of infection processes when the sputum cannot be obtained in children. Also immunocompetent patients and children with cystic fibrosis may be unable to produce sputum for microbiological analysis (11). BAL can be obtained in these children to investigate atypical mycobacteria and more reliable than sputum cultures. BAL ideally should be obtained before starting antimicrobial therapy but can be still infromative if the patient is unresponsive to treatment or deteriorating in spite of antimicrobial treatment.

The other important indication of BAL is to define the aspiration. Presence of significant number of macrophages heavily laden with lipid may support the diagnosis of aspiration (12). Pepsin in BAL samples is also indicative for aspiration. In lung transplant patients, BAL in conjunction with transbronchial biopsy is used to distinguish rejection from infection (13). However, BAL alone is not sufficient to have the diagnosis of rejection. Finally, BAL is also used for therapeutic removal of mucus plugs, blood clots and bronchial casts (14).

Whole lung lavage is another method of obtaining samples from lung and also therapeutic in pulmonary alveolar proteinosis and few other conditions. It rarely indicates in children and requires partial cardiopulmonary bypass or single lung ventilation.

Technique of BAL

BAL is effectively perfromed during FB. During the procedure, contamination of lower airway specimen with upper airway secretions should be avoided. Suction of the fluid should be done after the tip of the bronchoscope is passed through the most distal airway. Before the FB, selection of the site is decided based on clinical, radiologic and bronchoscopic findings. FB is directed to selected lobe and BAL is obtained from that lobe initially. If there is diffuse disease, BAL can be obtained from multiple lobes especially from lingual and right middle (5). After wedged to selected lobe, sterile saline is installed through suction channel and 1–2 mL of air is installed to clear the saline from the channel after each aliquot. During the suction of saline, extensive negative pressure should be avoided to overcome alveolar collapse. This causes not only insufficient sampling but also alveolar trauma.

The temperature of saline can be warmed up to body temperature (37 ℃) or keep in room temperature. There is no consensus about the number and volume of aliquots that used in BAL. In adults, 3 aliquots with 100 mL or 5 aliquots with 50 mL is recommended (15). Various protocols have been developed for children. Some of the bronchoscopists use standard volume of 10 to 20 mL in 2 to 4 aliquots regardless of the weight and age of the children. Some others adjust the volume of the aliquots based on body weight. Ratjen *et al.* suggested that 3 mL/kg of sample into 3 aliquots with maximum volume of 20 mL/kg can be used in children (16). In general, 40–60% of installed fluid is recovered and the remainder will be absorbed. The first aliquot is relatively rich in fluid from

the surface of the conducting airways and may have higher percentage of inflammatory cells. This sample can be used for cell count whereas remainder samples can be reserved for microbiological analysis. BAL sample fluid should be processed rapidly (less than 4 h) or keep at 4 ℃ until time to processing. Microbiologic studies including simple stains and special stains can be performed. Polymerase chain reaction (PCR) can be used to identify the pathogens and cytologic analysis including total cell counts, flow cytometry and lymphocyte subsets can be investigated.

Interpretation of BAL findings

Normal BAL fluids contain less than 5% of neutrophils and neutrophil counts can be detected up to 95% in bacterial infections (17). Less than 25% of neutrophil count is rarely indicates bacterial infection. Increased neutrophil counts can be associated with aspiration, asthma, cystic fibrosis, acute respiratory disease and alveolitis. Alveolar macrophages are most common non-epithelial cells in BAL fluids and constitutes 80–90% of cell counts. Lymphocytes are the second most common cells and composing 5–10% of total cells. Increased lymphocyte counts are not specific to a disease but significantly higher in sarcoidosis, *M. tuberculosis* infection, interstitial lung disease, hypersensitivity pneumonitis, *Pneumocystis jiroveci* infection and non-tuberculous mycobacterial infection (5). Eosinophils are rare in healthy children (0–1%) and higher in allergic and parasitic diseases. *Pneumocystis carinii* infection, interstitial lung disease and drug-induced lung disease also had elevated eosinophil counts in BAL samples (18).

Epithelial cells are common in BAL fluids. Squamous cells are from upper airways whereas ciliated columnar cells are from lower airways. *Staphylococcus aureus*, *Haemophilus influenza* and *Streptococcus pneumonia* with a concentration of more than 100,000 organism/mL of BAL fluid in association with elevated neutrophils are considered as evidence of infection. Absence of neutrophils, bacteria in BAL liquids present contamination rather than infection. However, density of bacteria more than 500,000 organisms/mL is considered as bacterial infection (5). Multiorganisms can be isolated from BAL of children with aspiration. Also, pathogens that are not normally seen in lungs, considered as infection regardless of numbers in immunocompromised children.

Therapeutic indications

Most of the therapeutic indications of bronchoscopy in children are restoration of airway patency. Although FB can be used for these indications, RB is superior to FB to remove foreign bodies and other interventional procedures. Foreign body removals are difficult and potentially dangerous. Favorable results were also reported with FB in small and peripherally located foreign bodies (19). However, it can be still difficult with FB. RB has several advantages such as requiring general anesthesia, assisted ventilation, larger instruments and greater variety of forceps (3). Foreign body aspiration may be seen with variable presentation ranging from subtle cough or recurrent pneumonia to a sudden fatal asphyxia. Diagnosis can be obtained by history, radiologic findings and physical examination. Most of the foreign bodies are non-radiopaque but some of them can be easily seen in chest X-rays (*Figure 2*). When clinical suspicion is achieved, bronchoscopy is indicated regardless of negative radiologic and clinical findings. Negative exploration rate is reported as 10-15% in several series (1). Foreign bodies can be easily detected and removed by use of RB with the help of ventilation-assisted technique (*Figure 3*).

Despite from foreign bodies, mass lesions such as granulation tissue and tumor lesions can be removed or biopsied with RB. Granulation tissue is the most common lesion result from foreign bodies, mycobacterial infection and mechanical trauma due to artificial airways. Also mucous blood clots are causes of atelectasis and can be removed with FB. Plastic bronchitis is a rare disorder characterized by formation of bronchial casts in the tracheobronchial tree with partial or complete airway obstruction. Serial RB is needed when plastic bronchitis is unresponsive to medical treatment or cause airway obstruction (20).

Mass lesions are rare in children. Bronchial carcinoids, hemangiomas and inflammatory myofibroblastic tumors can be seen during childhood (21). Benign and polypoid lesions can be resected with forceps and laser by the help of RB. Malignant tumors usually extend to bronchial wall and cannot be resected with bronchoscope. Transbronchial biopsy (TB) is available for histopathological diagnosis. TB is a potential bleeding procedure and RB has advantage for bleeding control over FB. TB is useful to evaluate the lung parenchyma and avoids need for thoracotomy. It can be especially carried out in patients with lung transplant with a sensitivity of 72–94% and specificity of 90–100% (3). However, it is not recommended for the diagnosis of idiopathic interstitial pneumonopathies in children in which open biopsy is indicated (22). Lasers with near-infrared and visible light spectrum are also used for the management of both benign and malign lesions (5).
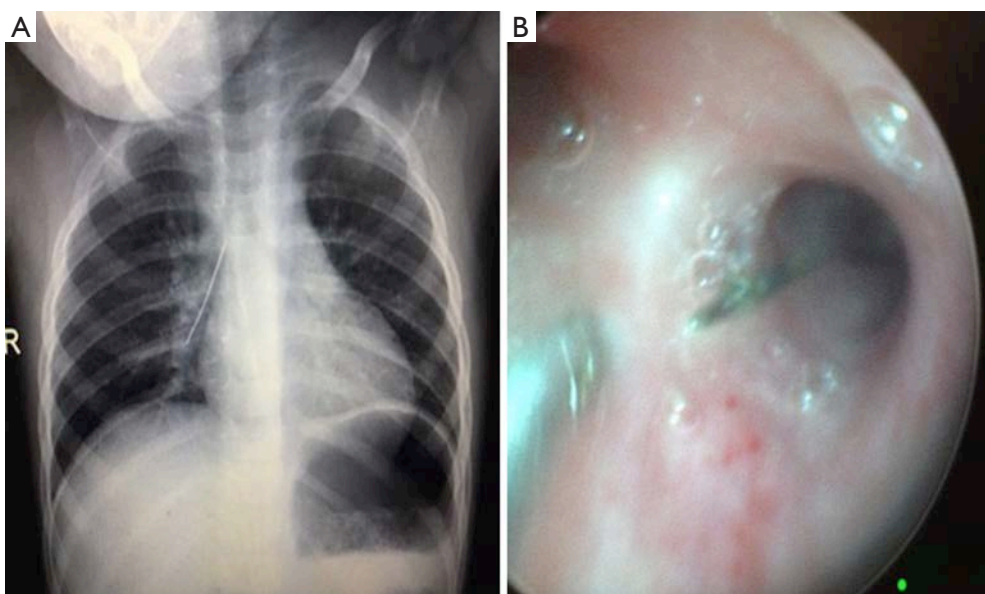
Figure 2 Chest X-ray showing foreign body (needle) in the right main bronchus. Foreign body removal by forceps.
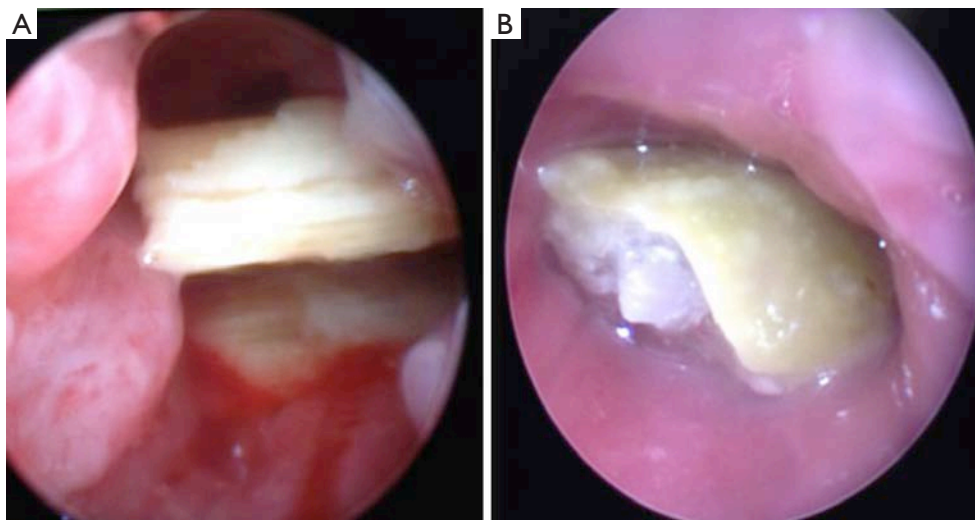
Figure 3 Foreign bodies obstructing main bronchus.

Tracheal and bronchial stenosis and severe malacia can be treated with the help of bronchoscopy. According to the nature of lesion, they can be dilated, lasered or stented (23,24). FB is also valuable in the management of difficult or complicated intubation. Intractable air leaks can be treated with Fogarty catheter, saline, fibrin glue or gel foam application.

Bronchoscopy can be done in conjunction with the surgery (25). Such as:

❖ To define position and cannulation of congenital or acquired tracheoesophageal fistulae;
❖ To define the effect of surgical manipulations intraoperatively during aortopexy and tracheopexy;
❖ To have selective bronchogram in case of localized bronchiectasis;
❖ Inspection of airways during the surgery.

Which type of bronchoscopy?

One of the most important issues is to define the

Table 4 Indications and type of bronchoscopy

Indications	FB	RB
Stridor	+	–
Persistent wheeze	+	–
Atelectasis	+	+ (may needed if remove the obstruction in airway)
Localized hyperinflation	+	–
Pneumonia	+	–
Persistent hyperinflation in patient who cannot produce sputum	+	–
Hemoptysis	+	+
Foreign body aspiration		
Known	–	+
Suspected	+	++
Persistent cough	+	–
Suspected aspiration	++	+ (to evaluate anatomy of posterior larynx and trachea)
Evaluation of patients with tracheostomies	++	+ (to evaluate anatomy of posterior larynx and trachea)
Suspected mass or tumor	+ (better for distal airway lesions)	+ (better for laryngeal and tracheal lesions)

type of bronchoscopy due to appropriate indication. Bronchoscopist should decide to use FB or RB to have the accurate diagnosis or to perform the best therapeutic intervention. *Table 4* summarizes the indications and options of bronchoscope types for each clinical problem.

Contraindications to bronchoscopy

There are no absolute contraindications for bronchoscopy; however, suitable indication, appropriate equipment and skilled personnel are mandatory to perform a safe procedure. Relative risk factors are cardiovascular instability, bleeding diathesis (thrombocytopenia or hypoproteinemia), severe bronchospasm and hypoxemia (5). Some of indications such as severe airway obstruction may increase the risk of complications.

Complications of bronchoscopy

Both FB and RB are safe procedures and complications are related with the patient's risk factors. Complications of RB are also due to instrumentation (bronchoscope itself), medication used and ventilation technique. Main complications are (3):

❖ Nasal trauma and epistaxis;
❖ Desaturation and hypoxemia;
❖ Cough and bronchospasm;
❖ Trauma and obstruction of airway due to edema;
❖ Hemorrhage;
❖ Pneumothorax;
❖ Fever and infections.

Fever can be seen 15% of patients especially BAL had been carried out during the procedure. It is related with cytokine release or with the transitory bacteremia.

Conclusions

In children, the most common indications for bronchoscopy are recurrent croup, chronic stridor and suspected foreign body. Bronchoscopy allows for examination of airway anatomy and dynamics. One of the most important role of bronchoscopy in the diagnosis of airway disease is obtaining samples from the airways. BAL samples are commonly used for differential diagnosis of several pulmonary problems. BAL findings should be carefully evaluated for the differential diagnosis. In addition to its diagnostic aid, bronchoscopy can be used for therapeutic indications. According to the indications and patient's needs, appropriate

type of bronchoscopy (FB or RB) should be chosen.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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The diseases of airway-tracheal diverticulum: a review of the literature

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Abstract: Tracheal diverticulum (DV) is a type of paratracheal air cyst (PTAC) that is often asymptomatic and usually detected incidentally by imaging methods. Tracheal DV are divided into two subgroups: congenital and acquired. Dysphagia, odynophagia, neck pain, hoarseness, hemoptysis, choking, and recurrent episodes of hiccups and burping can also be seen in symptomatic patients. Thin-section multidetector computed tomography (MDCT) is useful for diagnosis of tracheal diverticulum. The relationship between DV and tracheal lumen can be demonstrated by axial, coronal, and sagittal reformat multiplanar images. Bronchoscopy can also be used in diagnosis for tracheal DV. However, the connection between DV and tracheal lumen can not be shown easily with bronchoscopy. Conservative treatment is the preferred treatment in asymptomatic patients. Surgical or conservative treatment can be performed for symptomatic patients, depending on patient age and physical condition.

Keywords: Trachea; diverticulum (DV); thorax; multidetector computed tomography; tracheal diseases; chronic obstructive pulmonary disease (CODP)

Introduction

Paratracheal air cysts (PTACs) encompass various pathological entities, including tracheocele, tracheal diverticula, lymphoepithelial cysts, and bronchogenic cysts. The reported prevalence of PTACs ranges from 0.75–8.1% (1-3). Tracheal diverticulum (DV) consists of small air collections at the paratracheal area lined by ciliated columnar epithelium. Tracheal DV is commonly asymptomatic and incidentally detected by imaging methods. The incidence of tracheal DV is 2.4% (4). Tracheal diverticula are usually located at the right posterolateral region of the trachea (97.1%) and rarely located at the left side (2.9%) (4). Tracheal DV are divided into two subgroups: congenital and acquired. Congenital tracheal DV is seen more commonly in males than in females. Its diameter is smaller and its connection to the trachea is narrow. It is located 4–5 cm below the vocal cords or just above the carina (5). Congenital tracheal DV occurs due to developmental defects in the tracheal cartilage. Acquired tracheal DV may arise at any level and is typically wide-mouthed and larger in size than congenital DV. They occur due to long standing increased intraluminal pressure caused by chronic cough or chronic obstructive pulmonary disease (COPD) combined with a weakened tracheal wall (6).

Review

Epidemiology

Tracheal DV is a benign condition characterized by one or multiple invaginations of the tracheal wall (7). It is usually

located in the right posterolateral region of the trachea at the level between the T1 and T3 vertebrae. The mean tracheal DV size is 4 mm (ranging from 2–6 mm) (4). The wall of the tracheal DV can be thin or thick. Kurt *et al.* revealed that the mean age of patients with tracheal diverticulum was 58 years (range, 16–93 years) (4). Polat *et al.* (8) reported that the mean age of the patients with paratracheal air cysts was 55±16.6. They also reported no significant difference between the presence of PTACs and age. Kurt *et al.* (4) reported that tracheal DV is more common in men (64%) than in women (36%). However, Cheng *et al.* (9) and Buterbaugh *et al.* (2) reported that PTACs were found to be significantly more common in women than in men. There are several different studies in the literature evaluating the relationship between tracheal DV and airway or parenchymal lung pathologies. Goo *et al.* (1) demonstrated that tracheal DV and bronchial DV may be accompanied by COPD (emphysema, chronic bronchitis, and/or bronchiectasis). A study by Buterbaugh and Erly (2) found no association between the presence of emphysematous lung changes and PTACs. In addition, Kurt *et al.* (4) showed no significant association between tracheal DV and COPD. Polat *et al.* (8) demonstrated a statistically significant relationship between COPD and PACs. However, there was no relationship between primary or metastatic malignancies, pneumonia, and other pulmonary diseases and PTACs. Kurt *et al.* found that 84 out of 412 tracheal DV patients had a bronchial DV, and 72 out of those 84 tracheal diverticula cases were associated with COPD. They also demonstrated a significant correlation between COPD and bronchial DV (P<0.05).

Classification

Congenital tracheal DV is located 4–5 cm below the vocal cords or just above the carina; it is often located in the right paratracheal area (5). Also, it is smaller that of acquired DV, and it communicates with a small tract to the tracheal lumen. Congenital tracheal DV arises from a defect in endodermal differentiation during development of the membranous posterior tracheal wall or from a defect in the development of the tracheal cartilage during the sixth week of fetal life (10). Congenital tracheal DV affects the entire anatomy (respiratory epithelium, smooth muscle, and cartilage) of the trachea, and it is often filled with mucus. It is rarely associated with other congenital malformations, such as tracheoesophageal fistula (11).

Acquired tracheal DV can occur at any level, and it only includes respiratory epithelium. It does not affect the smooth muscle or the cartilage (1). It is frequently located in the posterolateral area at the level of the thoracic inlet between the extrathoracic and intrathoracic area. It is also commonly located in the posterolateral area between the extrathoracic and intrathoracic trachea at the entrance to the thorax, and it is larger than congenital tracheal diverticulum. Acquired tracheal DV can occur as a complication of surgical procedures or as a result of tracheomalacia. In addition, an increase of the tracheal intraluminal pressure caused by chronic cough or obstructive lung disease with emphysema combined with a weakened musculature of the trachea wall due to repeated respiratory infections can lead to the acquired form of tracheal DV (5). Acquired tracheal DV can be single or multiple. Multiple acquired tracheal DV is the hallmark of tracheobronchomegaly or Mounier-Kuhn disease (11,12).

Clinical presentation

Acquired and congenital DVs are often asymptomatic. Chronic cough, dyspnea, stridor, or recurrent tracheobronchitis may be seen in symptomatic patients (6). Dysphagia, odynophagia, neck pain, hoarseness, hemoptysis, choking, recurrent episodes of hiccups, and/or burping may also seen (6,13). Tracheal DV can also cause dysphonia due to recurrent paralysis resulting from direct compression of the DV. Infected tracheal DV may lead to paratracheal abscess (5,13). Tracheal intubation can be difficult in patients with tracheal diverticula. There was a case report of pneumomediastinum as a result of perforation of a tracheal diverticulum caused by tracheal intubation in the literature (14).

Diagnosis

Multidetector computed tomography (MDCT) is the best imaging method to demonstrate tracheal DV. It is useful for evaluating the localization, size, contour, and wall thickness of tracheal DV. Communication between the DV and trachea can also be seen with MDCT. Characteristic MDCT findings of tracheal DV include a thin-walled air sac at the paratracheal area with or without communication to the tracheal lumen (7). MDCT also can be use to distinguish between congenital and acquired lesions, depending on the presence or absence of cartilage and the
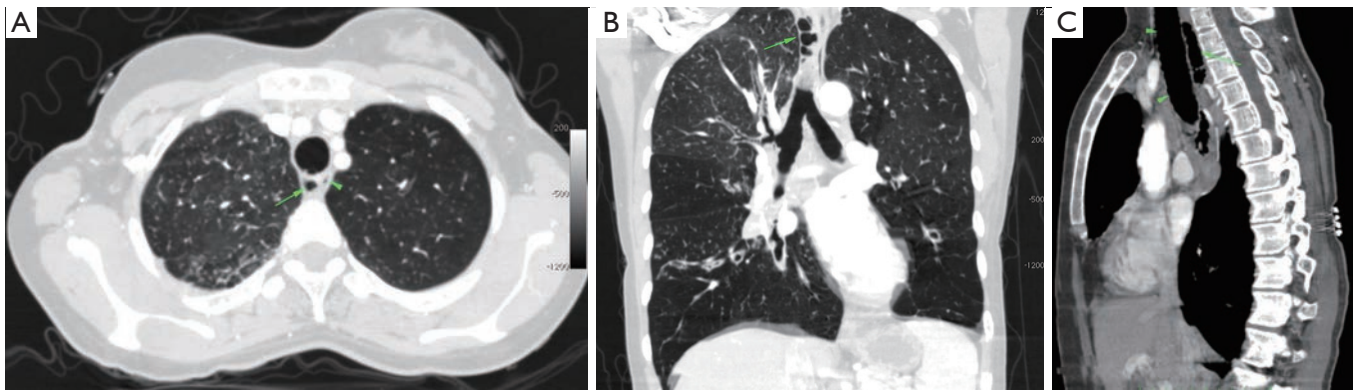
Figure 1 Contrast-enhanced multidetector computed tomography (MDCT), 1 mm thickness. (A) Axial images of the chest showing air-filled tracheal diverticulum (DV) located at the right posterior paratracheal area (arrow) adjacent to the esophageal lumen (arrowhead) in the mediastinal window. There is no visible communicating channel between the DV and the tracheal lumen; (B) coronal and (C) sagittal reformatted images of the chest show a lobulated multiseptated air-filled tracheal DV (arrow) located at the paratracheal area in the parankim window. In addition, peribronchial wall thickening and mild emphysematous changes are observed in the parenchymal window.
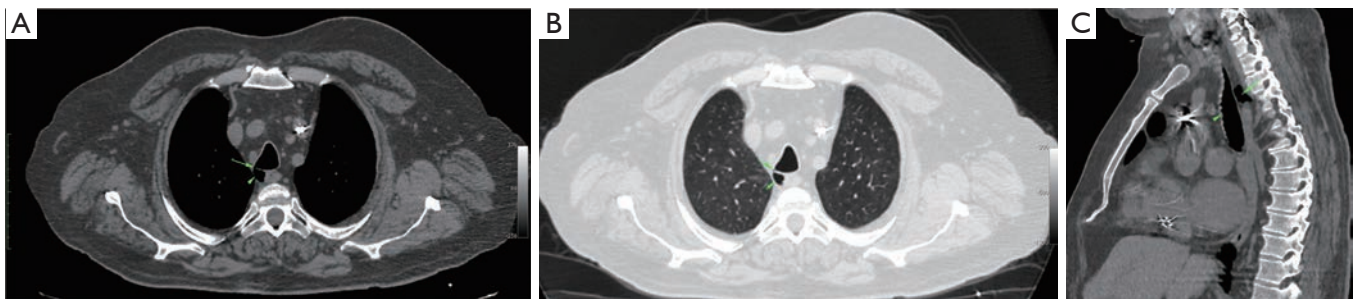
Figure 2 Contrast-enhanced MDCT, 1 mm thickness. The axial images of the chest reveal tracheal DV (arrowhead) at the right posterolateral aspect of the trachea in the (A) mediastinal and (B) lung window. The connection (arrow) between the tracheal lumen is also seen at the posterior wall of the trachea. Coronal (C) reformatted image of the chest demonstrates tracheal DV (arrow) at the posterior of the trachea (arrowhead). MDCT, multidetector computed tomography; DV, diverticulum.

size of the neck of the DV (5). Slice thicknes of the chest MDCT should be thinner than 1 mm for detailed, accurate evaluation of tracheal DV. Axial, coronal, and sagittal multiplanar images can be obtained with thinner (≤1 mm) slice thicknesses (*Figure 1*). Connection between DV and the trachea can be evaluated easily with these multiplanar images (*Figure 2*).

Kurt *et al.* (4) demonstrated communication between the tracheal lumen and diverticula in 53 (12.9%) of the 412 tracheal diverticulum cases. In addition, Polat *et al.* (8) demonstrated communication between the tracheal lumen and air cysts in 50 (16.6%) of the 301 PTACs.

Bronchoscopy can be used for diagnosis of tracheal DV; however, this is an invasive procedure. In addition,

tracheal DV with a very narrow opening or those joined to the trachea by only a fibrous tract may not be revealed by bronchoscopy (5). The finding of a collection of paratracheal air necessitates first determining whether its origin is tracheal or from another nearby structure. Differential diagnosis of PTACs include laryngocele, pharyngocele, Zenker's DV, apical hernia, and lung bullae (5). Pharyngocele and Zenker's DV can be differentiated from tracheal DV by barium studies or thorax MDCT. In addition, apical hernia and apical bullae can be distinguish from tracheal DV by thorax MDCT (15).

Tracheal DV can become infected due to recurrent upper respiratory tract infections, and infected tracheal DV can progress into a paratracheal abscess. Infected tracheal

DV can be viewed as a paratracheal mediastinal mass with a fluid-containing cyst that usually enhances following the intravascular administration of contrast materials in thorax MDCT. Infection may also progress into empyema or subphrenic abscess (13). Infected paratracheal diverticula cannot not be easily distinguished from infected Zenker's DV. If the connection between the tracheal lumen and the DV is not visualized in thorax MDCT or bronchoscopy, upper gastrointestinal system endoscopy should be performed. If previous studies are available, radiographic records can be compared (13).

Treatment

Treatment is not necessary in asymptomatic patients (9). The age of the patient, the clinical presentation, and the presence of comorbidities should be taken into account when choosing a treatment approach in symptomatic patients (16). Surgical resection is often the treatment of choice for young, symptomatic patients (9). Surgical resection can be performed with the lateral cervical approach without the need for thoracotomy. In addition, endoscopic cauterization with laser or electrocoagulation can be used to treat symptomatic patients (5). However, conservative treatment can be performed in older patients. Conservative management (antibiotics, mucolytic agents, and physiotherapy) may also be applied for these patients.

Patients with acquired tracheal DV cannot always benefit from surgical resection. Prevention of the infection of diverticulum is the optimum choice in patients with multiple and wide-based acquired tracheal DV (7). Surgical resection is needed for congenital tracheal DV due to the long-term accumulated mucous in the lesion, which could be a source of infection. Surgical resection should be performed carefully in these patients due to the risk of injury of the laryngeal nerve and the esophagus (7).

Emergency intubation and surgical drainage is indicated in patients with paratracheal abscess who present with respiratory distress (13).

Conclusions

Tracheal DV is a type of PTAC that is usually discovered incidentally on thorax MDCT. The connection between the trachea and DV is not always shown by imaging methods and bronchoscopy. There are two different types of tracheal DV: congenital and acquired. The differential diagnosis of congenital and acquired tracheal DV is important for treatment. Surgical resection is needed for congenital tracheal DV due to the long-term accumulated mucous in the lesion, which could be a source of infection.

Acknowledgements

Footnote

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Esophageal cancer revealing a tracheal diverticulum

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Abstract: Tracheal diverticulum is a benign entity characterized by single or multiple invaginations of the tracheal wall, and is rarely encountered in clinical practice but frequently in postmortem examination as an incidental finding. Its combination with esophageal cancer is extremely rare. In this case report, we present a patient with these two lesions and analyze their correlation.

Keywords: Esophageal cancer; tracheal diverticulum

Introduction

Tracheal diverticulum is a benign entity characterized by single or multiple invaginations of the tracheal wall (1). It is rarely encountered in clinical practice but frequently in postmortem examination as an incidental finding, because almost all patients are asymptomatic (1-3). The overall prevalence of tracheal diverticula has been estimated to be 1% in an autopsy series (1,2,4). Despite many reports about tracheal diverticulum, its combination with esophageal cancer is rare. In this case report, we present a patient with these two lesions and analyze their correlation.

Case presentation

A 74-year-old female was referred to our Hospital because of dysphagia. Over the past few decades, she occasionally suffered from mild dysphagia and laryngeal friction, especially when swallowing food at a mouthful. But in the past six months, the symptoms were intensified and sometimes mucous sputum occurred. No other obvious digestive symptom was present. She denied fever, chest pain, asthma, dyspnea, and obvious weight loss. Her parents, siblings and children have no history of similar diseases. She had no history of smoking and denied regular alcohol intake. Physical examination disclosed no abnormity except for scattered rhonchi in both lungs and laboratory examinations showed mild anemia. An upper endoscopy visualized with

esophageal scan revealed a stenotic lesion 24 cm from the incisors which was confirmed by barium contrast study. Pathology of the lesion (extracted by endoscopy) prompted esophageal squamous cell carcinoma.

The computed tomography (CT) scans of the neck and chest showed a 3.1 cm × 2.1 cm elliptic air-filled cavity, which was adjacent to the posterolateral wall of the trachea at the level of the T1 vertebral body, and wall thickening of esophagus at the T3 level (*Figure 1*). We did not find any connection between the diverticulum and trachea through bronchoscopy and CT, but we cannot deny the existence of some very small orifices between them or just some fibrous connections (*Figure 2A*). A week later, the esophageal carcinoma was surgically resected by thoracoscope through right chest and upper abdomen, while the gastric tube and esophageal stump were anastomosed at the left neck. We could touch the diverticulum and see its translucent smooth surface through the incision on the left side of the neck (*Figure 2B*). The diverticulum had not been treated surgically. The pathologic report confirmed the diagnosis of esophageal squamous cancer (ulcer type). Postoperative course was normal and significant improvement was observed 2 months after surgery.

Discussion

Tracheal diverticula can be divided into two types: congenital and acquired, and they are different in shape, structure, location, and medical histology (1). The congenital type
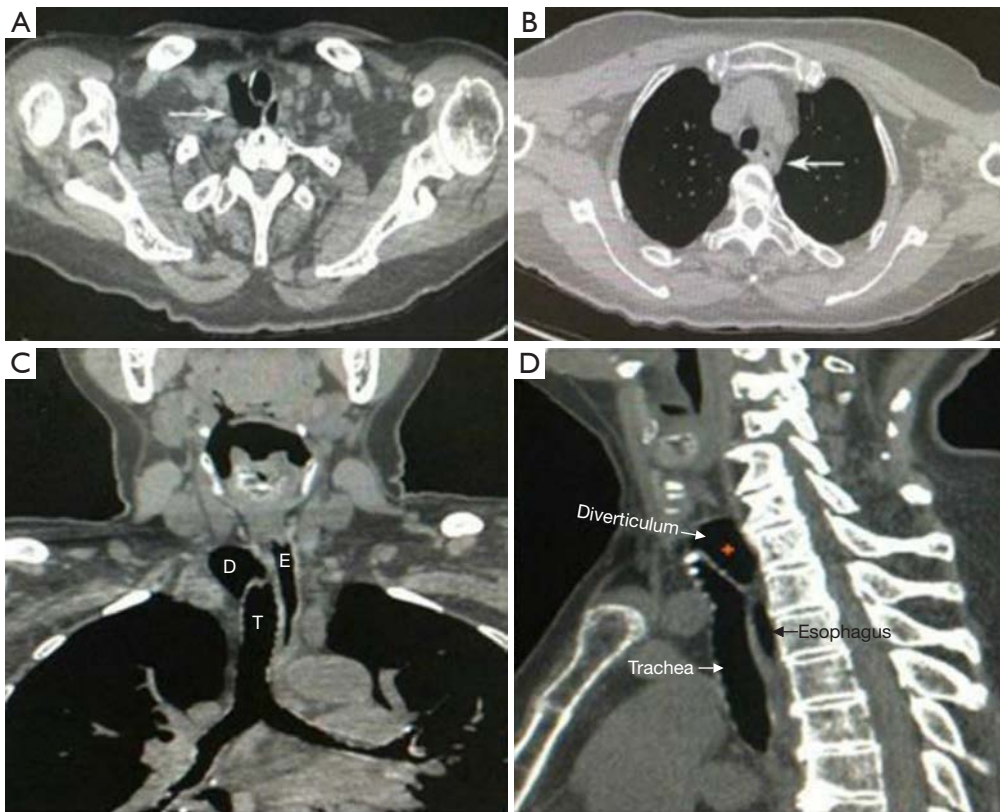
Figure 1 (A) Axial thin-section CT revealed a diverticulum located posterior, and to the right of the trachea (arrow); (B) esophageal wall of the lesion is thickened (arrow); (C) coronal CT image (D, diverticulum; T, trachea; E, esophagus); (D) sagittal CT image. CT, computed tomography.
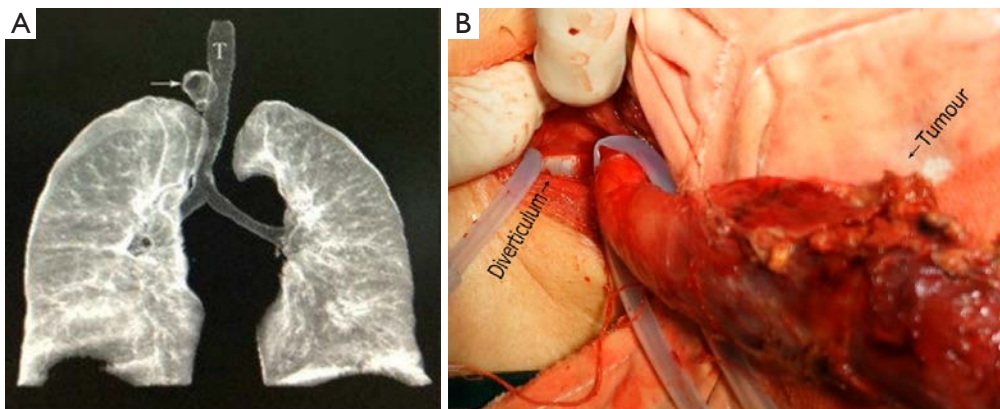
Figure 2 (A) CT 3D reconstruction of the trachea clearly revealed a tracheal diverticulum which is located to the posterolateral tracheal wall with no visible communication. (Arrow, the diverticulum; T, trachea); (B) intraoperative view of the esophageal lesion and the diverticulum at the left cervical incision. CT, computed tomography; 3D, 3-dimensional.

is considered to be a malformed supernumerary lung and generally consists of respiratory cartilage smooth muscle and epithelium, which is more common in men, and often appears on the right side of trachea, 4-5 cm below the vocal cords (1,4,5). Acquired tracheal diverticula are always larger than congenital ones, and result from increased intraluminal pressure caused by repeated coughing or obstructive pulmonary disease combined with a weakened trachea wall

due to respiratory trauma or chronic inflammation (6). Therefore, they can occur at any level and the wall in them is often composed of respiratory epithelium, without any cartilaginous or smooth muscular element.

Tracheal diverticula are usually incidental on radiographic or CT findings. Paratracheal air cysts were visible in only 14% of the study subjects on chest radiographs (4). The optimal modality for diagnosis seems to be a thin-slice CT of the trachea and 3-dimensional (3D) reconstruction, which provide information about the origin, size and connection of the diverticulum. On CT images, 98.5% of the paratracheal air cysts were located in the right posterolateral region, at a level between T1 and T3 vertebra, because this region is probably the point of least resistance at the limit of the intra and extra thoracic trachea (4,7). Differential diagnosis includes pharyngocele, laryngocele, pneumomediastinum, apical hernia of the lung and the other paratracheal air cysts (1-3). Furthermore, most tracheal diverticula are asymptomatic and tend to be incidentally detected. Nevertheless, a tracheal diverticulum filled of sputum and other secretions acts as a bacterial culture medium, leading to repeated respiratory infection and aggravating hemoptysis, stridor, or dyspnea. Rarely, a large diverticulum can compress the recurrent laryngeal nerve, resulting in dysphonia, or compress esophagus, giving rise to dysphagia. On the other hand, treatment options can be divided into surgical resection (rarely advocated but should be reserved for young or symptomatic patients), laser cauterization via rigid bronchoscopy, and conservative treatment (antibiotics, bronchodilators, mycolytic agents and physiotherapy in the elderly and debilitated patients). However, in clinic, specific intervention is usually not necessary for the majority of patients who are asymptomatic (1,3,4). Moreover, some large tracheal diverticula, especially posterior ones, can compress the esophagus thus result in dysphagia (2). In comparison, their tracheal diverticulum and our, have similar form, location and size. This conclusion may also explain why our patient experienced mild dysphagia for years. As far as we know, this is the first case report in which the patient had the combination of esophageal cancer and tracheal diverticula. Although no direct relationship was found between tracheal diverticulum and esophageal cancer through the adjacent tissues, we cannot deny that the dysphagia caused by esophageal cancer can be aggravated by the tracheal diverticulum. As for this case, the dysphagia was alleviated gradually after esophagectomy.

It is noteworthy that the operation should be avoided if the patient suffered from respiratory tract infection or foreign body retention in tracheal diverticulum detected by bronchoscope. Besides, an accurate positioning of the diverticulum by CT is helpful, and protection of the diverticulum during esophagectomy and lymph node dissection is mandatory as it is fragile and risky for perforation or even esophago-tracheal fistula. Additionally, resection of tracheal diverticulum could be considered if it was perforated during the surgery to avoid mediastinal infection. Furthermore, a shortened period of tracheal intubation after the operation is recommended to avoid ventilator associated pneumonia.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Subglottic tracheal stenosis

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Contributions: (I) Conception and design: A D'Andrilli; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: A D'Andrilli; (VII) Final approval of manuscript: All authors.

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Abstract: Benign subglottic stenosis represents a major therapeutic challenge. Interventional bronchoscopic treatment has a limited role in this setting due to anatomical and technical reasons. The benefit with these techniques is generally temporary, due to frequent recurrences, need for repeated procedures and risk of extending the area of damage. Laryngotracheal resection is at present the curative treatment of choice. Literature data show that surgical treatment may allow very high success rates at long term with low perioperative morbidity and mortality. Technical aspects and results are reported and discussed.

Keywords: Subglottic stenosis; laryngotracheal resection

The subglottic space at the cricoid level is the narrowest part of the airway. It extends from the inferior margin of the vocal cords to the lower border of the cricoid cartilage. Subglottic stenosis is generally benign and may be due to a variety of diseases, but post intubation (PI) injury is definitely the most frequent cause. Such injury may be produced by either translaryngeal intubation or tracheostomy (1-5). Translaryngeal intubation may result in damage involving both the glottis and the subglottis. This usually follows periods of prolonged intubation in intensive care units due to the need for mechanical ventilatory support (1-3). At subglottic level, following mucosal ischemia and ulceration produced by the rigid wall of the endotracheal tube, healing occurs with the formation of a firm fibrous scar resulting in varying degree of stenosis. Concentric stenosis is the most frequent finding. However, damage at the glottis and vocal cords most commonly involves the posterior structures with ulceration of the interarytenoid mucosa. This could be responsible for subsequent fibrous stricture in this site with possible extension to the cricoarytenoid joints and limitation of the vocal cords function. Isolated stenosis of the anterior commissure is more rare (3).

Other known causes of subglottic stenosis include airway trauma, inhalation burns and irradiation. A peculiar group of patients with subglottic stenosis is represented by those with idiopathic (ID) stenosis. This disease is characterized by an inflammatory cicatricial stenosis that occurs almost exclusively in women between the third and the fifth decade without other identifiable causes of airway stenosis (6). More rare causes are tracheal infections including bacterial tracheitis, tuberculosis, histoplasmosis and diphtheria, and collagen vascular diseases including Wegner's granulomatosis, relapsing polycondritis, polyarteritis and scleroderma (6).

Treatment of stenosis located in the subglottic region is a major therapeutic challenge. This poses increased technical problems with respect to treatment of lower tracheal stenosis, due to the need for approaching a disease involving the larynx near the vocal cords.

Surgical resections are the first line curative treatment although a number of less invasive alternative therapeutic options are available. Technical aspects and results are here reported and discussed.

Alternative treatments

Interventional bronchoscopic treatments including laser, mechanical dilation and stenting, whose application in tracheal surgery has greatly increased in recent years, have a limited role in subglottic stenosis due to anatomic and technical reasons (7). Literature data show that only simple stenosis including cases of thin web-like stricture or granuloma can be removed definitively by dilation, laser treatment or laser-assisted mechanical dilation. However, the benefit in more complex lesions is generally temporary, with frequent recurrences, consequent need for repeated procedures and risk of extending the diseased segment (7-9). Especially when a stent is placed, this can enlarge the area of airway injury and be responsible for further complications such as granuloma formation or prosthesis migration (7-8). Moreover, there is general agreement that the use of laser resection for subglottic stenosis should be limited as much as possible because of the risk for damaging the underlying cricoid cartilage (9).

In Brichet's experience, complex stenosis treated with laser and stenting as first approach obtained only a 17.6% success rate (10). The authors concluded that surgery is mandatory for such complex lesions and that interventional bronchoscopic procedure must be considered only in case of emergency to resolve acute respiratory failure due to critical stenosis or for temporary management while evaluating timing to surgery.

Similarly, Galluccio *et al.* (11) analyze results of their large series including 21 cases of subglottic stenosis and conclude that the endoscopic treatment of complex subglottic stenosis is generally contraindicated.

Looking at literature data, there is general convincement that good functional outcome can be obtained with bronchoscopic treatment of benign stenosis if the indication is restricted to tracheal disease excluding subglottic location (12).

Therefore, at present these techniques are mainly employed to stabilize the stenosis before surgery or to achieve an acceptable palliation in patients who are not suitable for surgery.

Temporary Montgomery T-tube and tracheostomy have been considered the only possible alternatives to surgery for a long time. However, these options have the disadvantage of potentially increasing the extent of the tracheal stricture and of favoring bacterial colonization (7). These two problems may be particularly detrimental for patients who are likely to be reconsidered for surgery thanks to improved general and/or local conditions.

Surgery

Historical notes and technical aspects

A stenotic disease involving the subglottic region presents increased technical problems when performing surgical treatment, principally due to the need to extend the resection to the cricoid cartilage, next to the vocal cords (*Figure 1*). Particular care must be taken when considering resection of the cricoid cartilage since the laryngeal nerves have access into the airway wall at the level of its posterior plate, whose upper border supports the arytenoid cartilages which play a major role in vocal cord function.

The initial experience of segmental resections of the cricoid cartilage was reported by Ogura and Powers in 1964 (13) and included a series of seven patients undergoing primary thyro-tracheal anastomosis. However, no attempt to preserve the laryngeal nerves was required since they were irreversibly damaged on both sides as a result of the trauma. In 1974 Gerwat and Bryce (14) described for the first time an original technique to preserve the posterior cricoid plate and the recurrent nerves above the level of the crico-thyroid joints by using an oblique line of resection in order to remove only the anterior cricoid arch. The upper transection line begins at the inferior border of the thyroid cartilage anteriorly and passes below the crico-thyroid joints posteriorly. However, this technique allowed a limited extent of resection of the posterior subglottic structures. Pearson *et al.* in 1975 (15) proposed a modification of this technique which allowed transverse resection of the subglottic airway at any level below the vocal cords, with preservation of a posterior shell of the cricoid cartilage sparing the laryngeal nerves. With this technique the line of division passes few millimeters below the vocal cords. Thus, primary thyro-tracheal anastomosis can be performed at less than 1 cm from the vocal cords. This is still the most frequently used technique to date. Before resecting the anterior portion of the cricoid arch, the trachea is sectioned below the stenotic segment, and the distal airway is intubated through the operative field by an armored endotracheal tube (*Figure 1*). When isolating circumferentially the diseased segment of the upper trachea there is generally no need to identify the laryngeal nerves (which are frequently involved in the surrounding scar tissue), since maintaining dissection close to the surface of the trachea can be sufficient to avoid injuries to these structures. The antero-lateral aspect of the cricoid cartilage is then freed completely from their perichondrial cover and resected (*Figure 1A*). A discrepancy in diameter between
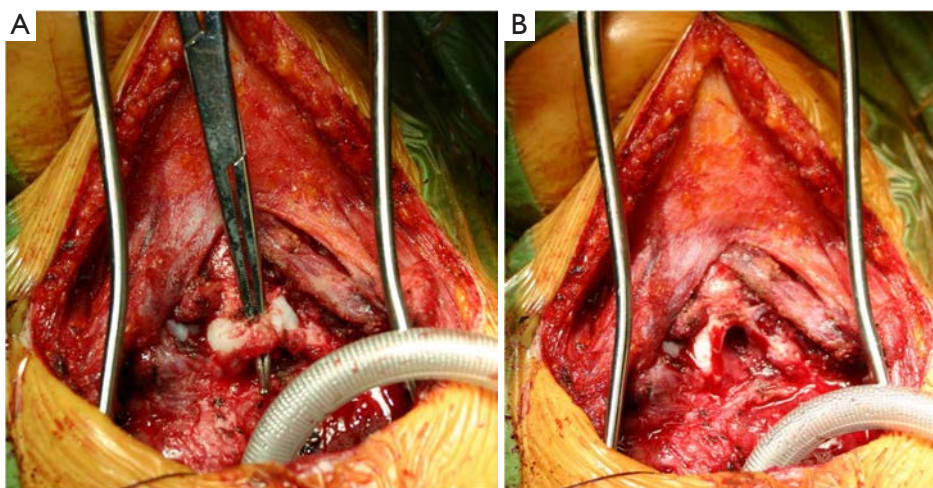
Figure 1 Intraoperative pictures of laryngotracheal resection for subglottic stenosis. (A) The anterior cricoid ring has been prepared for resection. The distal tracheal stump has been intubated through the operative field; (B) laryngotracheal resection including the anterior cricoid ring has been completed.

the lumen of the subglottic airway and the distal trachea at the time of reconstruction is unavoidable (*Figure 1B*). The end-to-end primary thyro-tracheal anastomosis is usually performed using interrupted sutures of 3–0 or 4–0 absorbable material [usually polydioxanone (PDS)]. Technical variation may include a running suture for the posterior membranous wall of the anastomosis.

Although Pearson and colleagues (15) suggested plicating the pars membranacea of the distal trachea to reduce this difference in terms of diameter, this procedure may be not necessary in many cases, since the elasticity of the distal trachea allows adequate compensation. In some patients the post-intubation subglottic stenosis may be complicated by glottic injury at the level of the posterior interarytenoid space. In such cases, when the interarytenoid scar is excised, a posterior mucosal defect is created. This defect can be covered by a pedicled flap of pars membranacea fashioned from the distal trachea and created by resecting one or two cartilaginous rings on the anterior aspect as described by Grillo (16).

Some other reconstruction techniques have been proposed in more recent years to manage laryngotracheal stenosis, especially when also the glottis is involved, with the aim of obtaining a permanent enlargement of the subglottic airway. These procedures, principally popularized by otorinolaryngologists, include the vertical division of the anterior wall of the thyroid cartilage and the posterior cricoid plate after resection of the anterior cricoid arch with the possible insertion of an autologous tissue graft between

the divided cartilaginous portions. Free pieces of bone or cartilage have been used as grafts.

Maddaus *et al.* (17) described a technique of laryngotracheal reconstruction indicated for stenosis close to the vocal cords (less than 5 mm) when their function is not compromised. Once the anterior cricoid arch is removed, the thyroid cartilage must be incised vertically in the midline to protect the vocal cords. Afterward, the affected mucosa is removed by incising the upper limit of the stenosis with the scalpel. The posterior cricoid plate can be then resurfaced by a membranous flap tailored from the distal tracheal stump.

A different technique has been described by Couraud (18-20). This is generally indicated for stenosis with current involvement of the glottis and compromised vocal cords function or in case of larynx cartilages damage by previous procedures (laser, tracheostomy, Montgomery T tube, surgery). In this operation after laryngofissure, the cricoid plate is incised and divided at the midline. Free cartilagine or bone graft can be interposed to enlarge the larynx lumen. The use of these techniques is more frequent in the pediatric population (21).

In the current authors' experience a variation of the standard Pearson technique with associated laryngoplasty was employed in some patients showing actual involvement of the vocal cords; after resection of the cricoid ring and crico-thyroid membrane, the thyroid cartilage was incised longitudinally on the midline for an extent of 1–1.5 cm (partial laryngofissure). The margins were then retracted

laterally to increase the airway space and the lower trachea was directly anastomosed to the retracted ends of the incised thyroid cartilage.

Perioperative management

Preoperative assessment is principally based on laryngotracheal endoscopic examination with the aim to evaluate mobility and trophicity of the vocal cords, severity and extent of the stricture, grade of inflammation and presence of edema or malacia. Laryngotracheal resection is generally performed after having assessed the stenosis stabilization endoscopically.

Completion of preoperative study with neck and chest computed tomography (CT) scan (spiral technique) is usually recommended to allow a more precise evaluation of the tracheal wall status (calcification, malacia) and of the extraluminal structures and tissue.

In patients with evidence of infection at the tracheostomy site, the present authors recommend systemic and local antibiotic treatment until sterilization proved by microbiology is achieved (7).

In cases of tight stenosis, some problems may arise at the time of intubation, before the resection; the stenosis can be dilated by a gum-tipped bougie or by a rigid bronchoscope. According to our experience (22), a small calibre (4–4.5) endotracheal tube can be passed through the stenosis in many cases of severe stricture, and this is usually sufficient for adequate ventilation until the trachea is exposed and incised allowing cross-field intubation. Occasionally the tube can be placed immediately above the stenosis.

Two strong chin-chest sutures are generally placed at the end of operation to maintain patient cervical flexion and are usually removed after 4–8 days depending on the length of the resected segment and on the anastomosis tension degree (22).

There is no general agreement among surgeons regarding the airway management at the end of the operation. Some authors (23,24) advocate immediate extubation in the operative room. According to this approach, if the patient is not able to breathe spontaneously or presents glottis edema, a small uncuffed endotracheal tube is left in site and removed after 48 to 72 hours. If the anastomosis is still a concern a small tracheostomy is placed two rings below the anastomosis.

Some other surgeons, including the current authors (18,22,25), use to leave a nasotracheal tube in place uncuffed in the awakened patient for 24 hours and then to remove it after bronchoscopic check of the anastomosis and vocal cords. The tube is kept with the tip distal to the anastomosis to protect it and to allow safe tracheobronchial toilette. In patients with postoperative glottis edema the tube can be left for a longer time while administering steroids.

When the thyro-tracheal anastomosis is performed very close to the vocal cords there is an unpredictable risk of post-operative glottic edema. This complication can be managed in different ways according to the surgeon's preference. Some authors recommend to place, at the end of operation, a small tracheostomy or a silicone Montgomery T-tube distal to the anastomosis (26). These can be left in place for a variable period of time: weeks or even months, depending on the status of the glottis and of the anastomosis. The present authors prefer to leave the naso-tracheal tube in place for a longer time (48–72 hours) after surgery while administering steroid therapy, since they have proved that with this strategy definitive extubation within few days can be obtained in almost all patients without sequelae (22).

Similarly, there is no consensus regarding the use of steroids after resection. In the present authors' practice the use of low-dose steroids is routinely considered during the postoperative course with the aim of reducing glottis and anastomosis edema. Over their long term experience no related impairment of the anastomosis healing has been observed (7,22,27).

According to the Massachussetts General Hospital group the use of steroids after laryngotracheal reconstruction should be avoided and limited only to cases of severe glottis edema with administration of short course high-dose therapy (24).

Patients' follow-up is principally based on clinical evaluation and tracheo-bronchoscopic controls (*Figure 2*). CT scan can be considered in selected cases when doubts on the tracheal wall status exist.

Results of surgery

Pearson and colleagues (15,17) reported the results of a series including 38 patients treated using their technique of partial cricoid resection and primary thyro-tracheal anastomosis. Recurrence of stenosis occurred in two patients and was successfully managed by re-resection in one case and by dilation and laser ablation in the other. There was no mortality. Ultimately, therefore, good results were achieved in all patients.

Grillo and coworkers (28,29) reported the outcome of 80 patients undergoing subglottic resection and

reconstruction with the use of their modified technique. Fifty of these patients had a PI injury. There was one operative death. All 49 survivors of this group presented satisfactory to excellent results.

One of the largest published experiences of laryngo-tracheal resection has been reported by Couraud and colleagues (30), which included 57 patients with post-intubation stenosis involving the subglottic region alone or in combination with the larynx out of a total of 217 patients with benign tracheal stenosis. Results were excellent or good in 98% of the cases. There was one perioperative death (1.8% overall mortality).
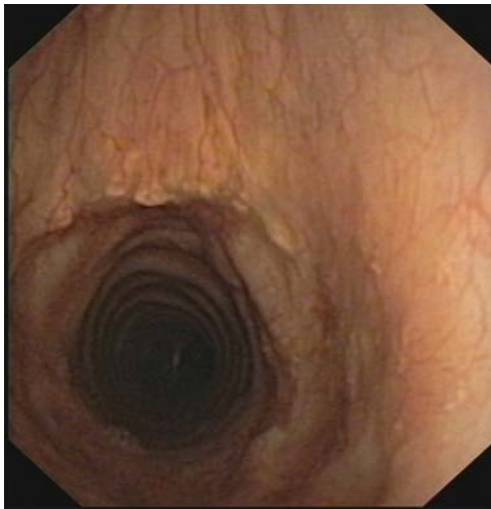
Figure 2 Broncoscopic check of the anastomosis 3 months after laryngotracheal resection.

To date single-staged laryngotracheal resection with primary end-to-end anastomosis has proved to offer the best option of cure for benign subglottic stenosis allowing definitive and stable high success rate. Major published series in this setting report good to excellent outcome in more than 90% of patients at long term with perioperative mortality under 1–2% (23,25,26,29-32). Major surgical morbidity is generally limited, with restenosis rates ranging between 0% and 11% (23,25,26,29-32), anastomotic dehiscence rates of 0–5% (9-16) and reoperation rate of 0–6% (13,25,26,29-32) (*Table 1*).

We have recently reported our experience of laryngo-tracheal resection for benign stenosis with the Pearson technique over a 25-year period reporting long-term results (mean follow-up 52 months) from a series of 109 consecutive patients (32). Resection of a tracheal segment longer than 4.5 cm was performed in 14 patients. Definitive extubation was possible in the first postoperative day in 98 patients. Four patients, after extubation at 24 hours, had to be reintubated within a few hours because of glottic edema. Definitive reextubation was possible, after steroid therapy, 2 days later in one patient and 3 days later in other two patients. One patient could not be re-extubated because of persistent glottis edema and received permanent tracheostomy. In six patients the nasotracheal tube was left in site for a longer time (2 days in four patients, 3 days in two patients) because of severe glottis edema visible at operation without need for further reintubation.

Immediate excellent or good anatomic and functional results were observed in 90.8% of the cases. Eight patients (7.4%) presented with recurrence of stenosis that was

Table 1 Main published series of patients undergoing laryngotracheal resection for benign stenosis in the last two decades

Authors [year]	Pts (n)	Diagnosis	Results		Restenosis (%)	Dehiscence (%)	Reoperation (%)	Mortality (%)
			Success (%)	Failure (%)				
Grillo *et al.* [1995] (29)	62	PI	92.0	8.0	8.1*	8.1*	0.0	2.4
Couraud *et al.* [1995] (30)	57	PI, PT, ID	98.2	1.8	0.0	1.8	0.0	1.8
Macchiarini *et al.* [2001] (31)	45	PI	96.0	4.0	4.4	0.0	2.2	2.0
Ashiku *et al.* [2004] (23)	73	ID	91.0	9.0	9.5	0.0	0.0	0.0
Marulli *et al.* [2008] (25)	37	PI, PT, ID	Early 89.0; definitive 97.0	Early 11.0; definitive 3.0	5.5	5.5	5.4	0.0
Morcillo *et al.* [2013] (26)	60	ID	Early 91.7; definitive 98.0	Early 8.3; definitive 2.0	3.3	3.3	6.7	0.0
D'Andrilli *et al.* [2015] (32)	108	PI, ID	Early 91.0; definitive 99.1	Early 9.0; definitive 0.9	7.4	0.9	0.0	0.0

*, restenosis + dehiscence. PI, post intubation; PT, post-traumatic; ID, idiopathic.

successfully treated by endoscopic procedures in all cases. This proves that even in patients experiencing early failure of the surgical procedure, final and durable success can be still obtained without reoperation. One patient (0.9%) presented with anastomotic dehiscence that required a temporary tracheostomy closed after one year with no sequelae. One patient (0.9%) with persistent glottis edema received permanent tracheostomy.

Definitive results at long-term were good or excellent in 94.5% and satisfactory in 4.6% of the patients. This series included 28 post-coma patients with neurological or psychiatric disorders that severely limited their cooperation in the postoperative period. Good to excellent outcome rates in this group were similar to those observed in the remaining population, suggesting that such condition should not be considered as absolute contraindication for surgery any more.

Published results of laryngotracheal resection associated laryngoplasty (Maddaus-type or Couraud-type techniques) for stenosis close to or involving the vocal cords are very limited and show wide variability among different studies. Systematic need for prolonged stenting after the operation is described with these techniques.

Maddaus *et al.* reported a series of 53 circumferential subglottic resections that included also 15 patients presenting with combined laryngeal and subglottic lesions (17). These complex stenoses were managed by synchronous subglottic resection and concomitant laryngofissure for laryngeal reconstruction according to the previously described technique. Decannulation and subsequent stable satisfactory results were achieved in all the patients of this subgroup but two. However, the need for temporary laryngotracheal stent (usually Montgomery T-tube) after laryngeal reconstruction was the rule with a duration ranging between 3 and 42 months.

McCaffrey (33) has reported a series of 21 patients with subglottic stenosis treated with the interposition of a costal cartilage graft in the anterior vertical incision of the cricoid and the thyroid cartilage. Although the incidence of satisfactory results was high (76%), there was a 24% rate of patients that could not be extubated. Terra (34) has published his experience of laryngotracheal reconstruction for glottic/subglottic stenosis using a laryngeal split with anterior and posterior interposition of a rib cartilage graft. Eighty percent of patients were completely decannulated after a mean of 23.4 months. A 20% tracheocutaneous fistula rate was reported in this series.

Particular interest has been reported in the literature when considering results of laryngotracheal resection for ID subglottic stenosis. This rare disease with unknown cause has been described by some authors (35) as potentially progressive, generally associated with severe inflammation which often involves the vocal cords or the space just below. Due to such characteristics, controversies still exist concerning the optimal management strategy and the appropriateness of surgical resection. Because of the high risk of leaving partially involved tissue with possible consequences for future recurrence, some authors believe that crycotracheal resection should not be indicated (35).

Dedo and Catten (35) after having analysed a series of 52 patients with ID stenosis concluded that this is a progressive disease that cannot be cured and hence advocated repeated palliative procedures indefinitely. In this experience all seven patients treated with resection had restenosis. The 43 patients undergoing only endoscopic treatments received an average of 8 procedures each, but 17 patients required permanent tracheostomy and only 21 patients appeared disease-free over the long term.

However, Grillo *et al.* in 1993 (6) reported a 91% rate of good to excellent outcome over a series of 35 single-staged laryngotracheal resections for ID stenosis. Similarly, Ashiku *et al.* (23) observed the same rate (91%) of patients with good to excellent long term results without need for further intervention. More recently, Morcillo *et al.* (26) in a Spanish multi-institutional study which included 60 patients receiving resection using different techniques (with or without postoperative temporary stenting) reported a 97% final success rate with no mortality.

In our series all 16 patients with ID stenosis undergoing laryngotracheal resection showed satisfactory to excellent long term results with no recurrence (32). Most of them presented with upper limit of stenosis and inflammation close to the glottis. Demanding excision of extra-mucosal scar tissue at the level of the cricoid cartilage was required in most cases, especially on the posterior plane with thyro-tracheal anastomosis performed close to the vocal cords. Based on evidences coming from our experience and other large series in the literature, we and other authors believe that single-staged laryngotracheal resection and reconstruction can be considered an effective definitive cure for such patients allowing stable long term results if the operation is perfomed with correct timing and adequate technical experience (23,26,32).

In conclusion results from the literature and from the present authors' experience confirm that laryngotracheal resection represents the curative treatment of choice for

benign subglottic stenosis allowing high success rates at long term. Most patients experiencing major postoperative complications can be successfully treated by non operative (generally endoscopic) procedures achieving stable results over time. Low compliance patients with neurologic and/or psychiatric disorders, and patients with ID stenosis show no increased failure and complication rates after surgical resection.

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Footnote

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Tracheal and bronchial stenoses and other obstructive conditions

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Abstract: Although tracheal stenosis and bronchial stenosis are relatively rare in the pediatric population, they are both associated with significant morbidity and mortality. While most cases of congenital tracheal stenosis in children present as complete tracheal rings (CTRs), other congenital tracheal obstructions are also encountered in clinical practice. In addition, acquired obstructive tracheal conditions stemming from endotracheal trauma or previous surgical interventions may occur. Many affected children also have associated cardiovascular malformations, further complicating their management. Optimal management of children with tracheal or bronchial stenoses requires comprehensive diagnostic evaluation and optimization prior to surgery. Slide tracheoplasty has been the operative intervention of choice in the treatment of the majority of these children.

Keywords: Tracheal stenosis; bronchial stenosis; complete tracheal rings (CTRs); slide tracheoplasty

Overview

Unlike subglottic stenosis, tracheal and bronchial stenoses are relatively rare in children and are generally congenital. Most pediatric tracheal stenosis manifests as complete tracheal rings (CTRs), with the absence of a membranous trachea extending for varying lengths of the airway. Other congenital malformations as well as acquired lesions are also encountered (1). Children with congenital tracheal or bronchial stenosis are frequently complex and can present with concurrent anomalies, including pulmonary artery sling, ventricular septal defects, lung hypoplasia, lung agenesis, and gastrointestinal defects (2,3).

Our article will briefly describe tracheal and bronchial stenoses and other obstructive conditions, presenting an overview of their diagnostic workup. We will subsequently present a succinct description of techniques used for surgical repair and the optimization of patients to ensure optimal surgical outcomes.

Diagnostic workup

Varying degrees of respiratory distress can be observed in patients with tracheal or bronchial stenosis. This may be accompanied with retractions and distal airway sound. Stridor, a "barking" or brassy cough, and "washing machine" airway sounds may be present. Dependent on the level of involvement, stridor may be inspiratory, expiratory or biphasic. Cyanosis and dying spells trigger urgent action (4).

Patients with severe tracheal stenosis may need urgent treatment because of life-threatening airway obstruction. On the other hand, asymptomatic patients with mild stenosis may not require surgical repair.

Diagnosis is frequently delayed because of the rarity of the lesion or because other more apparent associated malformations draw the attention of the clinician. For this reason, experience and a high level of clinical suspicion are essential in establishing an accurate diagnosis (5).

Bronchoscopy remains the most important tool to the

diagnosis of tracheal and bronchial stenosis. Both flexible and rigid instrumentation can be used to determine the type of lesion, localization, extension, and severity (5).

Imaging can provide excellent definition of an abnormal tracheobronchial tree and its mediastinal counterparts. A CT scan provides good anatomic delineation of the airway and magnetic resonance imaging (MRI) enables full assessment of the vascular structures and their relationship to the adjacent trachea. Nevertheless, definitive assessment requires endoscopic evaluation.

Congenital tracheal stenoses

CTRs

Although CTRs are rare, they are the most common cause of congenital tracheal stenosis. In children with this anomaly, the cartilaginous rings are circular and smaller than the unaffected trachea. This anomaly is characterized by the absence of a membranous trachea and the trachealis muscle.

More than 75% of patients have other associated anomalies, which can be severe; these include pulmonary artery sling, cardiac defects, and lung hypoplasia or agenesis. A large series conducted at Cincinnati Children's Hospital Medical Center [2011] revealed that 60% of patients with CTRs had cardiovascular abnormalities, most commonly a pulmonary artery sling (1).

Four specific patterns of CTRs may be recognized. These patterns include (I) complete rings that are relatively patent proximally but come down to a very small distal ring near the carina; (II) the "stovepipe" airway with a long segment of CTRs of similar diameter; (III) a short-segment stenosis, often in the mid-trachea; and (IV) CTRs associated with a high pig bronchus (6,7).

Infants typically present with increasing respiratory distress, stridor, retraction, apnea, cyanosis, and occasionally, dying spells. Some children present with a "wet" sounding airway due to secretions adhering to the area of stenosis, sometimes described as "washing machine respiration". Symptoms are exacerbated when the infant is agitated or when feeding (4).

In the first few weeks of life, the infant may grow at a far greater rate than the stenotic airway. This occurrence may result in critical obstruction. Reports of a very difficult intubation with the need to "screw in" the endotracheal tube are unfortunately quite common. This can further exacerbate airway edema and may cause a compromised

airway to become a critical airway (4).

A small percentage of children with CTRs do not present until later in life. Moderate obstruction can accommodate growth without causing respiratory distress (8). As the child grows, so do the CTRs, though at a non-linear rate. Symptoms in these children develop when the growth of the child significantly exceeds the growth of the airway. Presentation typically manifests with exercise intolerance and is insidious in nature. Important to note, a child may have comparatively few symptoms despite a significantly narrowed airway.

Assessment is made with rigid bronchoscopy, which should be performed with extreme care. The smallest possible telescopes should be used, as rough instrumentation in the area of stenosis may cause enough swelling to convert a narrow airway to a critical airway, necessitating abrupt emergent intervention. An estimate of the size of the airway is valuable. Because 50% of the children with CTRs have a tracheal inner diameter of approximately 2.0 mm at the time of diagnosis, the smallest endotracheal tube (2.0 mm) and the smallest tracheotomy tube (2.5 mm) cannot pass through the stenotic segment without severe damage to mucosa or tracheal rupture. Intubation proximal to the complete rings is sometimes advisable. If intubation is still not able to maintain adequate ventilation, typically seen with severe distal tracheal involvement, or when there are coexistent cardiovascular anomalies requiring repair, extracorporeal membrane oxygenation (ECMO) may be necessary to stabilize the child.

In view of the high proportion of patients with other congenital anomalies, a computed tomography (CT) scan and an echocardiogram should be performed. CT scans should be performed with contrast and 3D reconstructions to best appreciate the anatomy of both the airway and surrounding vasculature.

Not all pediatric patients with CTRs require tracheal reconstruction. In some asymptomatic or mildly symptomatic patients, a period of observation helps in determining whether a tracheoplasty will ultimately be required (5,8,9). A small number of patients show evidence of significant airway growth and do not require surgery. In other cases, the growth of the child will be faster than the growth of the CTRs, with the child becoming more symptomatic over time. In this clinical scenario, intervention will ultimately be required. In general, the younger the age at initial presentation, the more likely the need for tracheoplasty (8).

When surgical repair is necessary, slide tracheoplasty is

currently the operation of choice (1).

Tracheal cartilaginous sleeve

In this condition, the trachea is not composed of 15 to 20 separate rings, but of a single sheet of cartilage that may extend proximally into the cricoid and progress distally into the bronchi. This is universally associated with craniosynostosis (Pfeiffer, Crouzon, or Apert syndromes) (10). While in most cases the sleeve trachea is not stenotic, in rare cases the posterior cartilaginous trachea may overlap, requiring operative reconstruction. In this setting, slide tracheoplasty is an effective reconstructive option; however, it is technically more challenging to perform (4).

Absent tracheal rings

Absent tracheal rings are an extremely rare intrinsic tracheal defect manifesting as tracheal stenosis or collapse. This condition typically presents in an otherwise normal child with a short-segment of the trachea (2 to 3 rings) missing cartilage. This segment is usually just proximal to the carina. Presentation is similar to CTRs; however, bronchoscopically, the stenotic segment lacks cartilage and is therefore distensible (11). This anomaly is generally managed with either a tracheal resection or a slide tracheoplasty (1,11).

Chondrodysplasia punctata

Chondrodysplasia punctata comprises a group of rare congenital disorders characterized by punctate calcification of cartilage referred to as "stippling"; this results in bone and skin lesions as well as ophthalmologic and cardiac malformations (12).

Laryngeal and tracheal calcifications in affected children are rarely reported. There is no universal management approach for these exceedingly rare anomalies. Balloon dilation of the trachea can be attempted. In refractory cases, tracheostomy should be considered (12).

Other congenital tracheal obstructions

Tracheal agenesis

Tracheal agenesis is a rare embryologic anomaly that almost always results in death. Patients who are prenatally diagnosed and in whom the atresia involves only the proximal trachea occasionally survive through the use of an *ex-vivo* intrapartum treatment (EXIT) procedure, low tracheotomy, and eventual tracheal reconstruction. In another form of tracheal agenesis, there is either a very short remnant of distal trachea, or the entire trachea is absent and the bronchi come directly off the esophagus. Neonates present at birth with severe respiratory distress. Temporary ventilation is often possible with esophageal intubation, and ventilation through a tracheoesophageal fistula; however, this is typically unsustainable. If there is no communication between the airway and the esophagus, congenital high airway obstructive syndrome (CHAOS) will result (13).

Type 4 laryngotracheoesophageal cleft

The triad of husky cry, aspiration pneumonia, and feeding problems in newborns with congenital anomalies should prompt an early workup for complete laryngotracheoesophageal cleft. Early surgical intervention is necessary to prevent aspiration and offers the only hope for survival (14).

Tracheomalacia

It is critical not to confuse malacia with stenosis, as the management of this disease is fundamentally different from the management of tracheal stenosis.

Overall, tracheomalacia is the most common congenital abnormality of the trachea. Diffuse tracheomalacia can be caused by intrinsic problems of the trachea, as in the mucopolysaccharidoses (Hunter and Hurler syndromes), but more commonly is localized. Children treated with prolonged mechanical ventilation for respiratory distress syndrome are particularly at risk (15,16).

In patients ultimately requiring tracheotomy, four levels of focal tracheal injury may induce cartilage damage and collapse: the suprastomal tracheal ring, the stoma, the overinflated cuff site, and the site of a malposition tip.

Most patients with tracheomalacia are asymptomatic. When symptomatic, however, children typically present with medium-pitched expiratory stridor. A "brassy" or "honking" cough may also be present. Despite the cough, the patient may have difficulty expectorating secretions. The most serious symptoms of tracheomalacia include dying spells and cyanosis.

In addition to the symptoms and signs attributed to tracheomalacia, the patient is often symptomatic from

a variety of associated anomalies. Commonly associated abnormalities include laryngeal clefts, tracheoesophageal fistulae, and bronchomalacia (15). Fifty percent to 75% of patients with tracheomalacia have concurrent gastroesophageal reflux disease (GERD) (17,18).

As with other tracheal anomalies, the gold standard in the diagnosis of tracheomalacia is endoscopy with the patient spontaneously breathing. This can be accomplished during flexible bronchoscopy or microlaryngoscopy and bronchoscopy using a rigid telescope. However, large-caliber rigid instruments may artificially stent open the tracheal airway, not appreciating the degree of anterior-posterior collapse. Therefore, many endoscopists prefer the use of flexible bronchoscopy to diagnose malacic conditions. If the plan of anesthesia is too deep and the patient is not spontaneously breathing, assistive ventilation will obscure disease as well (4).

In all circumstances, intervention should be based on the symptoms of the child rather than the appearance of the airway. Nonoperative management includes pneumatic stenting of the airway with continuous positive airway pressure (CPAP), positioning, and treatment of GERD, which has been shown to exacerbate laryngotracheal disease (19).

Operative management obtains the best results for symptomatic localized lesions. Clinical circumstances that mandate operative intervention include persistent symptoms that fail nonsurgical therapies, acute life-threatening events, recurrent pneumonia, and other manifestations of intermittent respiratory obstruction. Currently, aortopexy is preferred for mid-to-distal tracheomalacia (20-22). Stents can be applied endoscopically to maintain tracheal patency across focally collapsed segments. Although they do not require open neck incisions, their propensity to migrate, to cause mucosal erosions, and to form granulation tissue makes them less attractive as a permanent solution (23). Alternatively, stents may be most effectively used as a temporizing measure while the collapsed segment gains intrinsic strength or while a more extensive repair is being planned.

Tracheotomy with or without positive pressure ventilation is frequently performed for intractable tracheomalacia that does not meet criteria for, or has failed, lesion-specific surgical therapy. The other common indication for tracheotomy is tracheobronchomalacia, as this is rarely amenable to surgical intervention. Severe tracheobronchomalacia may require long-term ventilation through the tracheotomy tube.

Vascular compression

Although vascular compression is not uncommon, the majority of affected children are either asymptomatic or mildly symptomatic. When symptomatic, children present with biphasic stridor, retractions, a honking cough, and dying spells.

Forms of congenital vascular compression affecting the trachea include innominate artery compression, double aortic arch, and pulmonary artery sling (4).

The diagnosis of airway compression is best established with rigid bronchoscopy. Thoracic imaging assists in determining the relevant vascular anatomy.

CPAP frequently offers a degree of temporary improvement, as segmental tracheomalacia may be present in the region of the vascular compression. Intubation or tracheostomy may be required to stabilize the airway prior to definitive treatment, but both should be utilized with caution because of the risk of forming an arterial fistula from erosion in the area of compression.

The surgical management of symptomatic vascular compression must be individually tailored to address specific pathology. Although alleviating vascular compression improves the airway, it takes time for the cartilage in the affected segment of the airway to completely normalize. Until the airway normalizes, children may require a tracheostomy (4).

Acquired tracheal stenoses

Acquired tracheal stenosis is generally traumatic in origin, either the result of direct injury (e.g., clothesline injury) or more commonly the result of trauma from the cuff or tip of an endotracheal tube. It is therefore usually a problem affecting the cervical trachea and amenable to a cervical approach if reconstruction is required (4).

Tracheal stenosis may also occur at the site of a tracheotomy, with either an A-frame deformity or suprastomal collapse due to cartilage disruption, erosion, and deformity at this site.

Patients with acquired tracheal stenosis have a tendency to present insidiously and have moderate complaints of exercise intolerance or sleep-disordered breathing. Their endoscopic exam often reveals a much more severe stenosis than their symptoms portend. These patients may present months to years following prolonged intubation, laryngotracheoplasty, or direct injury to the airway (4).

Congenital bronchial stenosis and other rare bronchial obstructions

Congenital bronchial stenosis

Isolated congenital bronchial stenosis is an unusual lesion, caused by compressive vascular anomaly, cardiac anomaly, or a congenital pulmonary cyst. The stenosis is usually seen in the left main bronchus, which is compressed between the left pulmonary artery and the descendent aorta. Symptoms and treatment vary depending on both the severity and anatomic location of the lesion. The diagnostic workup, including bronchoscopy, CT scan, and echocardiography, is similar to that used for suspected tracheal stenosis (24).

Although extremely rare, complete bronchial rings may also occur. They are usually an extension of CTRs. Butler *et al.* reported that 23.7% of their patients with CTRs have extension of the stenosis into one or both bronchi (2).

Surgical management of bronchial stenosis includes resection and reconstruction of the bronchus and slide bronchoplasty, and this can be extremely challenging in babies because of the small size of the infant airway (7,24). Postoperative complications are common after bronchial surgery. Atelectasis is the most frequent complication, followed by stenosis, anastomotic leakage, malacia, pneumonia, and empyema (24).

Other rare bronchial obstructions

Congenital bronchial lobar agenesis is characterized by either complete termination of the bronchus or significantly stenosed segmental or lobar bronchus. Bronchial obstruction results in enlargement of the peripheral bronchus, mucus accumulation, and emphysematous changes in the peripheral lung. Prenatal diagnosis remains difficult, but unlike tracheal agenesis, this disease is compatible with life (25). Most patients can be managed nonoperatively.

Absent bronchial rings (Williams-Campbell syndrome) are a rare disorder characterized by deficiency of subsegmental bronchial cartilage and the development of airway collapse and bronchiectasis that may subsequently progress to respiratory failure and death (26). Some published reports suggest a familial association (27). The bronchoscopic findings are characteristic, and reconstruction requires transection of the bronchial insertion at the carina, splitting the distal posterior wall of the bronchus and the proximal anterior wall of the trachea

and sliding the bronchus further up the trachea (4).

Acquired bronchial stenosis

Because of selective intubation of the right main bronchus, acquired stenosis in neonates is likely more frequent than congenital stenosis of the major bronchi; nevertheless, it is rare. Most cases can be managed with endoscopic balloon dilation or laser resection.

Acquired bronchial obstruction may also occur following vascular intrathoracic procedures, mainly because of a cardiovascular stent compressing the bronchus.

Preoperative optimization

Optimal management of children with tracheal stenosis requires comprehensive evaluation prior to repair. The temptation is to proceed straight to definitive repair should the child deteriorate. However, if the airway permits intubation with a 2.0 endotracheal tube, this should be performed via nasotracheal route in order to temporarily stabilize the child. When this approach is not possible, an endotracheal tube sized to accommodate the cricoid cartilage, but placed shallow, and proximal to the complete rings, can still permit positive pressure ventilation. It is rare that the first two tracheal rings are affected in children with CTR, and therefore most children can be intubated proximal to the complete rings. If ventilation remains difficult, ECMO is advisable but should not be taken lightly. Clearly, tracheotomy is rarely helpful as the smallest CTRs tend to be more distal, and the smallest available commercial tracheotomy tube is 3.6 mm in outer diameter. More importantly, tracheotomy may further compromise the options of subsequent operative repair (4).

All patients should undergo methicillin-resistant *Staphylococcus aureus* (MRSA) screening and treatment before the surgery. MRSA infection in open airway procedures can be a devastating complication, resulting in dehiscence, graft loss, and weakening of the cartilaginous structure of the laryngotracheal complex (28).

Although GERD plays an important role in the pathogenesis and prognosis of laryngeal stenosis, its impact on children with tracheal or bronchial stenosis is insignificant.

Surgical management

Surgical correction may not always be necessary in infants with tracheal or bronchial stenosis. These patients

may, however, present later in life with dyspnea; in this clinical scenario, surgical correction becomes essential. Concomitant cardiac or great vessel anomalies that require repair, most often a pulmonary artery sling, require a combined procedure through an anterior sternotomy with the patient under cardiopulmonary bypass to repair the trachea. A cervical approach to the trachea, without sternotomy or bypass, may be performed in patients with mid- to high tracheal lesions.

Endoscopic techniques

Although balloon dilation and laser resection can be performed in some cases of acquired tracheal stenosis and in some children with postoperative complications (29), its role in the treatment of congenital tracheal stenosis is controversial. Most authors agree that endoscopic techniques should not be employed in patients with CTRs (5).

Open surgical procedures

Tracheal resection

Tracheal resection with primary reanastomosis is required much less frequently in children than in adults. Historically, this procedure in children was considered to be less successful than in adults because of the smaller airway diameter in children and less tolerance of anastomotic tension (7). This technique is a useful tool for addressing short-segment CTRs (involving less than one-third of the trachea) and acquired stenosis of the trachea, and careful surgical technique and selection of patients have been shown to improve outcomes (30). However, it is not uncommon to discover a longer segment of CTRs following dissection of the trachea during an open procedure. Therefore, in our experience, optimal results have been achieved with a short segment slide tracheoplasty (4).

When performing a tracheal resection, one must avoid anastomosis close to the carina because any anastomotic problems may ultimately require placement of a tracheotomy tube; the tip of the tracheotomy tube must lie between the anastomosis and the carina and this may be problematic if there are only 2 to 3 mm between the anastomosis and the carina (4).

Augmentation techniques

Costal cartilage graft tracheoplasty

This procedure is reserved for upper tracheal stenosis,

since the strap muscles are not present in the lower trachea. Overlying muscle provides the vascular supply to cartilage grafts, and an intrathoracic graft may require a pedicled muscle flap to remain viable. Because cartilage grafts treating intrathoracic tracheal stenosis have an increased risk of granulation tissue formation at the site of the graft and the risk of prolapse of the graft into the airway (4), we no longer perform this procedure.

Anterior pericardial patch

For many years, pericardial patch tracheoplasty was the standard procedure for the management of CTRs. It is effective in children with mild to moderate stenosis due to CTRs. However, children with more severe forms of tracheal stenosis tend to have a difficult postoperative course following this procedure; this is usually due to granulation tissue in an airway that remains small despite the tracheoplasty or anterior malacia of the patch (4). This operation has fallen out of favor given the established success of the slide tracheoplasty for most cases of CTRs.

Tracheal autograft patch

This technique involves the resection of the middle third of a segment of CTRs, anastomosis of the upper and lower ring segments, and splitting of the remaining rings anteriorly. The resected segment of rings is then laid open and used as an anterior graft through the remaining rings (31). It is superior to the pericardial patch; however, it is associated with a significant incidence of restenosis.

Slide tracheoplasty

Slide tracheoplasty was originally described by Tsang *et al*. (32) and popularized by both Grillo *et al*. (7) and by our team at Cincinnati Children's Hospital (6). This operation overlaps stenotic segments of the trachea, shortening it but doubling the diameter of the stenotic area. Slide tracheoplasty is currently the operation of choice for tracheal stenosis attributed to CTRs. This technique has a high rate of success and minimal morbidity (1).

This technique has a number of advantages relative to other methods. These advantages include immediate tracheal reconstruction with rigid, vascularized tissue with a normal mucosa; ability to extubate patients early in many cases; less postoperative granulation tissue formation; and growth potential of the reconstructed trachea (7,33). In addition, it is a versatile technique: one can perform a short-segment slide, an oblique slide, or even an inverse slide if circumstances dictate. The slide can also extend into the membranous

trachea or into the carina if required. The whole length of the trachea may be slid, even past the carina.

Briefly, patients are initially placed on cardiopulmonary bypass, with cannulation of the ascending aorta and the right atrial appendage. If a pulmonary artery sling is present, this is repaired prior to the slide tracheoplasty. The trachea is exposed by dissecting between the ascending aorta and the superior vena cava. In the process, removal of the right paratracheal lymph nodes facilitates tracheal exposure. The carina is identified deep to the right pulmonary artery and the anterior trachea is exposed from the carina to the upper aspect of the CTRs (1,4).

Intraoperative bronchoscopy is then performed to define the upper and lower limits of the complete tracheal ring segment. A 30-gauge needle is placed through the anterior tracheal wall as it is visualized by the bronchoscope to define the proximal and distal CTRs. At this point, with the patient stabilized on cardiopulmonary bypass, a more comprehensive evaluation of the distal airway can also be performed (1,4).

The length of the stenosis is then measured and the trachea is transected at the midpoint of the segment of complete rings. Each end of the transected trachea is then mobilized. The lateral vascular attachments to the trachea are preserved in this process. The anterior wall of the proximal tracheal segment is incised vertically. The posterior wall of the distal segment is cut vertically toward the carina. Cartilage is then trimmed from the corners of the proximal and distal segments, and the segments then slid over each other. Depending upon the length of the stenotic segment, this requires additional tracheal mobilization from both superior and inferior attachments. The carina is displaced superiorly as stay sutures applied to the distal trachea are attached to the head drape (1,4).

The anastomosis is performed with a running 5.0 or 6.0 double-armed polydioxanone suture (PDS), with a single knot securing the repair proximally. Prior to final closure of the anastomosis, the patient is re-intubated with an age-appropriate endotracheal tube, and the tip of the tube positioned under direct visualization. The anastomosis is then leak tested, and further sealed with fibrin glue. The proximal and distal extent of the anastomosis can be marked with small hemoclips to help identify the extent of the anastomosis on post-operative radiographs. The patient is then removed from bypass, the chest closed, and the patient is transferred to the intensive care unit. Even with near full-length tracheal reconstruction, it is unusual to need a suprahyoid release or chin to chest sutures.

Extension of the slide into a bronchus or cricoid cartilage has been performed successfully at our institution and may assist with repairing these concomitant stenoses. In children with an associated pig bronchus, a modified slide can also be performed, with the rings being split oblique to the midline, so as not to compromise the orifice to the bronchus (1,4).

At Cincinnati Children's, we have followed this surgical approach since 2001. Our experience has demonstrated that the slide tracheoplasty with cardiopulmonary bypass support can be performed with very low mortality despite the complexity of this patient population. Also, the slide technique requires airway reintervention less frequently than other techniques (1).

In our last cohort study (n=80), 29% of our population required airway reintervention within 12 months of the initial procedure. However, this rarely involved more than endoscopic management, such as balloon dilation, endoscopic resection of granulation tissue, or temporary stent placement. Four deaths (5%) were reported (1). This mortality rate was much lower than the previously reported mortality rate of up to 24% in some series (34,35).

A series of 101 children who underwent a slide procedure at Great Ormond Street Hospital was published in 2014. Seventy-two of their patients (71.3%) had associated cardiovascular anomalies. Thirty-three children (33%) had residual stenosis at 3 months and 8 (8%) had residual stenosis at 9 months after the surgery. Stenting was required in 21.8%, mainly in patients with preoperative bronchomalacia. The mortality rate was 11.8%, and bronchomalacia and the need of preoperative ECMO were associated with this outcome (2).

Regarding the anesthetic technique, although current methods, including jet ventilation, may allow for repair of distal and long-segment tracheal stenosis, these can often be obtrusive and cumbersome for the surgeon. Cardiopulmonary bypass is a safe alternative that allows partial deflation of the heart and lungs so that exposure of the complete trachea is optimized. Conversion of ECMO to cardiopulmonary bypass is also recommended for the procedure for this same reason. Successful surgical management thus depends upon close collaboration of the airway surgeon and the cardiovascular surgeon.

Cervical slide tracheoplasty without cardiopulmonary bypass has also been performed by airway surgeons at Cincinnati Children's since 2003. It is considered to be a valuable technique that should be added to the surgical armamentarium for patients requiring open airway

reconstruction. This procedure is an adaptation of the standard slide procedure and can be used for tracheal long-segment stenosis, tracheal "A-frame" deformities, and multilevel laryngotracheal stenosis. In our cohort published in 2012, we described 29 patients who underwent this procedure. Operation-specific success rate was 79% (23 of 29 patients), including all 10 patients with long-segment acquired tracheal stenosis. Lower operative success occurred in patients with concomitant subglottic stenosis, posterior glottic stenosis, and multilevel airway lesions. Four patients (14%) experienced complications: one patient had a minor wound infection; one had a dehiscence that was managed with a revision tracheoplasty; one had an innominate artery injury that was successfully treated intraoperatively without sequelae and one had a symptomatic "figure-8" deformity that required revision therapy (36).

A retrospective series by Matúte *et al.* (n=10) compared the slide procedure with anterior costal cartilage graft tracheoplasty (ACCGT) for the treatment of CTRs, reporting that all six patients treated by ACCGT experienced restenosis while the four patients treated with slide tracheoplasty were asymptomatic and doing well (33).

Complications that occur after slide tracheoplasty most commonly reflect the underlying health status of the child. These infants may be critically ill prior to tracheal repair, and often remain critically ill following tracheal repair. The tracheal repair may also cause problems, including granulation tissue along suture lines and restenosis or collapse at the anastomosis site. Temporary or permanent injury to the recurrently laryngeal nerve is also possible. Failure of extubation usually results from one of these issues. A worrisome complication is dehiscence of the anastomosis. However, this is extremely uncommon. Granulation tissue is usually amenable to serial bronchoscopic management. Stenosis or collapse at the anastomosis site may require either periodic dilation of the trachea or placement of a tracheotomy tube, with the tip of the tracheotomy tube bypassing the area of concern (4). However the primary predictors for poor outcomes were revision surgery, unilateral pulmonary agenesis, and bronchial stenosis.

Postoperative care

Following open tracheal repair, the aim is extubate the child at the conclusion of the procedure, or within 24–48 hours. While the patient is intubated in the pediatric intensive care unit, the child's head is maintained in forward flexion on a pillow, and it is advisable to maintain peak ventilation pressures below 30 cm of water pressure so as not to damage the anastomosis. Ideally, chest drains are left in place until after the extubation. In the setting of an extremely unstable preoperative ventilated child, postoperative ECMO may be required. The aim is to establish endotracheal ventilation and remove the child from ECMO as soon as possible (1).

Follow-up endoscopy to examine the repair is routinely performed 1 and 2 weeks after the operation. Gentle balloon dilation is sometimes useful during the recovery phase if the figure-8 tracheal deformity at the repair is significant. This intervention helps prevent left and right lateral suture lines from coming into contact and adhering (1). Children without cardiopulmonary anomalies are typically discharged from the hospital 2 to 3 weeks postoperatively.

Acknowledgements

Footnote

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Current concepts in severe adult tracheobronchomalacia: evaluation and treatment

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Abstract: There is increasing recognition of tracheobronchomalacia (TBM) in patients with respiratory complaints, though its true incidence in the adult population remains unknown. Most of these patients have an acquired form of severe diffuse TBM of unclear etiology. The mainstays of diagnosis are dynamic (inspiratory and expiratory) airway computed tomography (CT) scan and dynamic flexible bronchoscopy with forced expiratory maneuvers. While the prevailing definition of TBM is 50% reduction in cross-sectional area, a high proportion of healthy volunteers meet this threshold, thus this threshold fails to identify patients that might benefit from intervention. Therefore, we consider complete or near-complete collapse (>90% reduction in cross-sectional area) of the airway to be severe enough to warrant potential intervention. Surgical central airway stabilization by posterior mesh splinting (tracheobronchoplasty) effectively corrects malacic airways and has been shown to lead to significant improvement in symptoms, health-related quality of life, as well as functional and exercise capacity in carefully selected adults with severe diffuse TBM. A short-term stent trial clarifies a patient's candidacy for surgical intervention. Coordination of care between experienced interventional pulmonologists, radiologists, and thoracic surgeons is essential for optimal outcomes.

Keywords: Expiratory central airway collapse (ECAC); severe diffuse tracheobronchomalacia (TBM); tracheobronchoplasty (TBP)

Expiratory central airway collapse (ECAC)

The tracheobronchial tree is a dynamic conduit that changes lumen size with exposure to varying pressures experienced during different phases of respiration. We will use the term ECAC to define the narrowing of the central airways during expiration and describe two different pathophysiologic entities, excessive dynamic airway collapse (EDAC) and tracheobronchomalacia (TBM). EDAC is a condition characterized by inward bulging of the atrophic muscular fibers in the posterior airway membrane during

exhalation with narrowing of the cross sectional airway lumen, whereas TBM is characterized by weakness of the anterior tracheobronchial cartilage wall that may present with or without excessive dynamic invagination of the posterior membranous wall (1-3). Though airway malacia can present as an isolated segmental weakness of the trachea, or, less commonly of the bronchi alone, the focus of this review article is the severe, diffuse form of acquired TBM that affects the central airways more globally.

Severe TBM is an acquired condition, and progression to its diffuse form has been described by a study of
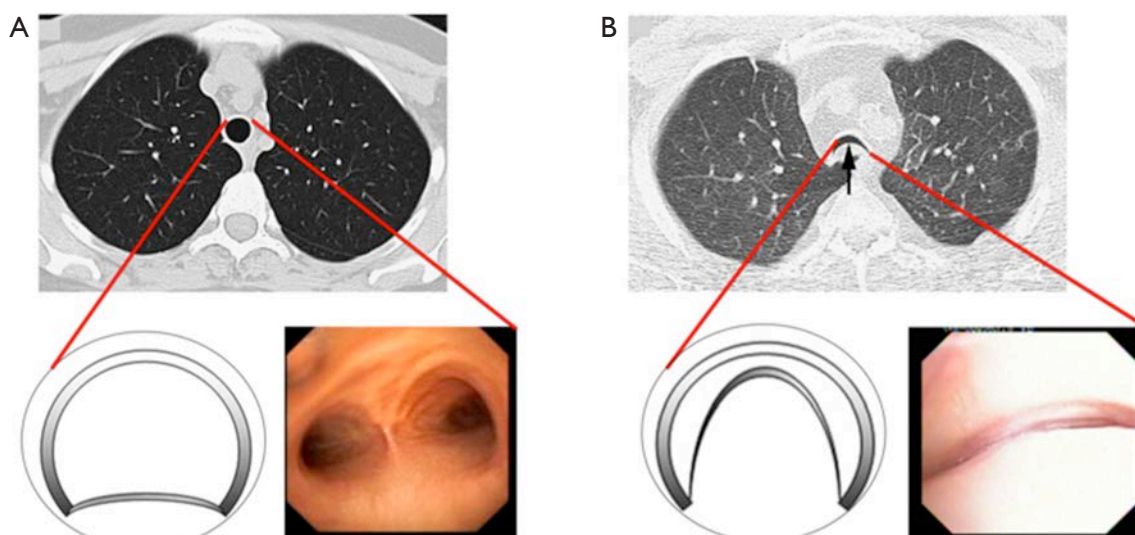
Figure 1 Schematic representation of (A) normal airway and (B) malacic airway pathology. Representative cross section images obtained during dynamic computed tomography (CT) scan and dynamic bronchoscopy accompany the airway diagrams.

bronchoscopic surveillance in patients with either isolated tracheomalacia or bronchomalacia in whom 67% and 100% of the patients, respectively, evolved to diffuse TBM during a mean follow-up interval of 5 years (4,5). This pathologic collapse of the posterior membrane produces dynamic outflow obstruction leading to symptoms such as dyspnea, orthopnea, intractable cough, and inability to clear secretions, predisposing the patient to recurrent infections (6,7). In addition, respiratory failure or failure of ventilator weaning may be the herald event that leads to a diagnosis of TBM (8,9).

TBM is an increasingly recognized abnormality of the central airways in patients with respiratory complaints, though its true incidence in the adult population as a whole remains to be elucidated. Estimates vary. For example, TBM has been identified in 1–4.5% of all patients undergoing bronchoscopy, but it has been reported to be present in more than 13% of patients who undergo evaluation for respiratory symptoms, and in as many as 23% of patients with a diagnosis of chronic bronchitis (6,10,11). One main reason for the wide range of estimates of the incidence of TBM in the general population is the ongoing debate over the definition of the extent of airway collapsibility and morphology required to meet the threshold for pathologic collapse. The currently accepted threshold for excessive airway collapse is a greater than 50% reduction in airway cross-sectional area with expiration (2,3). Under this definition, greater than 13% of patients with emphysema were found to have TBM on examination. When the

threshold was raised to greater than 70% airway collapse, however, only 5% met the definition of TBM (12).

Recent work from our institution has demonstrated a wide range of expiratory tracheal collapsibility observed in healthy volunteers, with many asymptomatic individuals frequently exceeds the current diagnostic threshold for TBM (13,14). These observations indicate that there is physiologic range of dynamic airway collapse in the tracheobronchial tree and that the diagnosis of TBM should not be made solely by the identification of >50% expiratory collapse in the cross-sectional area of the airway lumen. In addition, it is important to emphasize that factor such age and gender should be considered when assessing forced expiratory airway collapse for suspected TBM (15). Consequently, when evaluating patients with suspected TBM are evaluated at the Complex Airway Disease Center of the Beth Israel Deaconess Medical Center (BIDMC) we restrict the categorization of severe TBM to patients with complete or near-complete collapse (>90%) of the central airways (*Figure 1*).

Etiology and classification of ECAC

The cause of diffuse TBM is often unknown, but it is frequently seen in patients with common respiratory conditions such as asthma, chronic bronchitis and emphysema. Most adults diagnosed with TBM have acquired forms of the disease, but there is a smaller subset of

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adult patients who have congenital tracheobronchomegaly (Mounier-Kuhn syndrome) which is not identified until adulthood (7). The etiology of acquired forms of TBM may be divided into inflammatory conditions, such as relapsing polychondritis (RP) and exposure to toxins (e.g., mustard gas) and compressive processes, including thyroid goiters, vascular abnormalities, and others (3,6,16). However, as previously mentioned, the etiology of TBM in most adult patients remains unknown.

The classification of ECAC has been the subject of multiple prior reviews (1-3,7) and is not the scope of this article. Several facts, however, are worth of mentioning. Malacic airways can be classified according to the morphology on inspiratory and expiratory images into three different subtypes: saber sheath-type TBM, circumferential-type TBM, and crescent-type TBM (17-19). Other authors have proposed subdividing airway collapse into two separate groups according to their mechanical etiology, distinguishing purely malacic airways from airways that only demonstrate membranous wall collapse as exhibiting either physiological collapse (dynamic airway collapse) or pathologic collapse (EDAC) (1,2). Although the physiology of airway mechanics is different for each entity, the clinical features of and therapeutic goals for TBM and excessive dynamic airway collapse are similar. Patients with severe excessive dynamic airway collapse refractory to medical management are candidates for surgical central airway stabilization to prevent excessive narrowing during exhalation.

We consider both airway cartilaginous wall and posterior membranous collapse as clinically significant forms of dynamic airway collapse. This is of particular relevance as the more pertinent consideration for clinical success of central airway stabilization seems to be less whether it is the cartilaginous or membranous wall pathology that potentiates collapse, but whether the presenting morphology is frown-shaped on expiration or lunate-shaped on inspiration, both of which are amenable to surgical stabilization.

Diagnostic interventions

The diagnostic evaluation of TBM can be challenging, as patients often have other concomitant chronic pulmonary conditions such as asthma or chronic obstructive pulmonary disease with overlapping symptoms. The mainstays of diagnosis are dynamic CT and dynamic bronchoscopy with forced expiratory maneuvers.

Dynamic flexible bronchoscopy (20) is currently the gold

standard for diagnosing TBM since it permits real-time examination of the airways and accurately captures dynamic airway properties, with reproducible valid results in regard to information on morphology, degree, extent, and location of pathology (21). At BIDMC, patients undergo bronchoscopy under minimal sedation using intravenous midazolam and fentanyl to allow them to follow commands. Oral anesthesia is accomplished using 10–20 mL of 1% atomized lidocaine to suppress gag reflex. In addition, and 1% lidocaine in 2-mL aliquots are delivered through the bronchoscope during the procedure to irrigate the vocal cords, aryepiglottic folds, and entire tracheobronchial tree. The patients are placed in supine position. Typically, an Olympus BF P180 video bronchoscope (Olympus America, Melville, NY, USA) with a 4.9-mm outer diameter and 2.0-mm working channel is used to minimize any stenting effect. The bronchoscope is introduced into the proximal trachea at the level of the cricoid. At this point, patients are instructed to inhale deeply, hold it and then forcefully exhale (forced expiratory maneuver). Samples of imaging are obtained at six different locations in the tracheobronchial tree (proximal trachea, mid-trachea, distal trachea, right main stem bronchus, bronchus intermedius and left main stem bronchus) and evaluated for degree of luminal narrowing in the anteroposterior diameter (9,21).

In addition, dynamic flexible bronchoscopy facilitates the detection of coexisting pathology such as vocal cord abnormalities or bronchitis and permits biopsy of the mucosa as well as sputum sampling for histological and microbiologic analysis. Despite the inherent subjectivity of evaluating luminal collapse endoscopically, recently we have demonstrated a favorable inter- and intra-observer agreement in estimating degree of central airway collapse associated with TBM amongst pulmonologist from different institutions (20). However, expertise in this technique is not present nationwide.

Dynamic expiratory CT is a highly sensitive method for detecting airway malacia and has been shown to be concordant with dynamic flexible bronchoscopy (3,22); it is an effective, noninvasive test for diagnosing TBM. A prospective, multicenter trial comparing dynamic expiratory CT and dynamic bronchoscopy would be helpful to assess the reproducibility of our findings across multiple centers. Such a study will help to determine the prevalence of malacia among patients with chronic nonspecific respiratory symptoms and to assess the specificity of dynamic CT for diagnosing TBM. Both modalities are useful in describing the morphology, severity, and distribution of the disease.

A caveat with either technique, however, is the potential variability in the effort of dynamic expiration, either because of inconsistent coaching of the forced expiratory maneuver or inconsistent compliance of patients with these instructions.

Pulmonary function testing is often unhelpful in screening patients during the initial diagnostic workup. A great proportion of patients may not achieve the predicted maximum forced expiratory flow while a substantial number of patients (21%) with moderate to severe TBM can demonstrate normal flow-volume loops (23). In our practice, the primary use of pulmonary function tests is to assess the degree of pulmonary comorbidity before intervention for TBM, and thus, the likelihood of an arduous or complicated recovery from tracheobronchoplasty.

Preoperative evaluation and stent trial

Once diagnosis of severe, diffuse TBM is established, and correlation of the deranged anatomy with significant symptoms and impaired quality of life is made, the patient is considered for treatment. Patients undergo physiologic assessment with pulmonary function testing and a 6-minute walk test. Standardized questionnaires are also administered to determine functional status (Karnofsky Performance Scale); symptomatology [modified Medical Research Council (mMRC) dyspnea scale]; and quality of life assessment [respiratory impacted quality of life (St. George Respiratory Questionnaire)] and Cough Specific Quality of Life Questionnaire (CQLQ) (9,16,21,24).

Our institutional protocol for preoperative evaluation of patients under consideration for tracheobronchoplasty is shown in *Figure 2*. Of note, it is important not only to confirm the extent and severity of TBM but also to maximize medical therapy for comorbidities such as obstructive airway disease. Routinely, patients undergo evaluation for vocal cord dysfunction and gastroesophageal reflux disease (GERD). If found, these diagnoses require adequate treatment prior to surgical evaluation. Previous observations from our group have revealed that GERD seems more prevalent in patients with TBM as compared with the general population and it may negatively impact the outcome of surgical tracheobronchoplasty (25,26). However, follow up studies are warranted to fully corroborate this correlation and thus, optimize the evaluation approach for patients with diffuse TBM.

At BIDMC, a Y-shaped silicone tracheobronchial stent is placed in advance of a patient's assessment for candidacy for surgical intervention (9). The stent is deployed within the airway portions that would be stabilized by a surgical tracheobronchoplasty—namely the thoracic trachea and left and right main stem bronchi, but not the cervical trachea, distal lobar or segmental bronchi, or smaller airways. After a two week trial, patients are evaluated for the level of symptomatology improvement attributable from stabilization of the central airways. Improvement of dyspnea is the most consistent metric of treatment effect, likely because dyspnea is the most common presenting complaint in patients with diffuse TBM and because of the immediate effect of the stent on expiratory airflow.

Notably, iatrogenic symptoms related to the stent may develop and detract from the perceived subjective sense of benefit that the patient might have with stent stabilization of the airway. Mucus plugging may occur in up to 36% of patients, and this might obscure the patient's subjective improvement in dyspnea (9,16). The stent may ease the barking cough associated with TBM, but this may be substituted by a cough secondary to the irritating effect of a foreign body in the airway. In similar equivocal fashion, secretions may be expectorated more easily with the stent in place, but the volume of sputum production might be increased by the presence of the stent within the airway lumen. In some instances, the stent trial may prove inadequate or impossible to complete in patients with unusually large or small airways if correct stent sizes is not available, or in patients in whom their anatomy impedes rigid bronchoscopy for Y-stent placement (e.g., extreme cervical kyphosis). To lessen these potential confounding outcomes, our group recently has piloted the use of uncovered self-expanding metallic stents for short-term trials (24,27). Despite these limitations, a planned short-term (<2 weeks) stent trial still may yield useful information about those patients with diagnosed TBM who may respond best to surgery. In our experience, between 60% and 75% of patients with TBM will respond to the stent trial in positive fashion, and improvement in symptoms, quality of life and exercise capacity following definitive surgical airway stabilization with tracheobronchoplasty is seen in 80% of these selected patients (21,25).

Tracheobronchoplasty: technical aspects and surgical results

The objective of surgical management is to stabilize the membranous wall of the intrathoracic trachea, both mainstem bronchi and bronchus intermedius. The
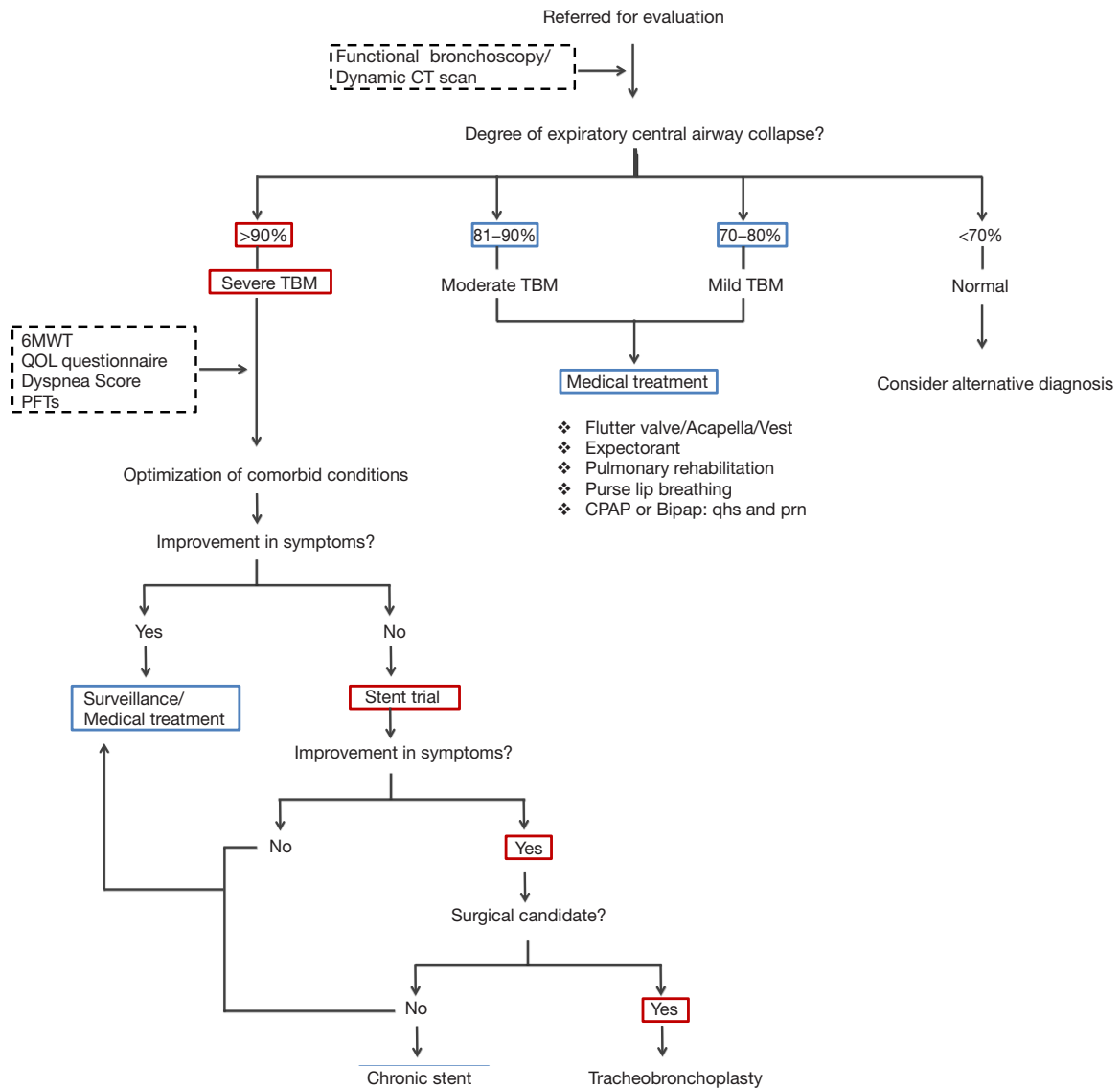
Figure 2 Beth Israel Deaconess Medical Center (BIDMC) Institutional protocol for evaluation of patients with severe diffuse tracheobronchomalacia (TBM).

redundant posterior membranous wall is plicated and fixed to the posterior splint by suturing a knitted polypropylene mesh to reconstitute the airway morphology and prevent intrusion of the membranous wall into the lumen of the airway (*Figure 3*). With time, the mesh is incorporated by fibrosis, with subsequent stiffening of the posterior membranous wall. The suture placement is also carefully selected to achieve tension across the membranous wall. The operation has historical roots going back over 50 years (16,29) and the BIDMC technique has been described in detail elsewhere (25). It is worth noting that

concentric forms of ECAC do not respond to this posterior stabilization.

In brief, left lung ventilation is established using a modified double-lumen endobronchial tube created by shaving off the tracheal lumen before placement in order to decrease airway distortion caused by the endotracheal tube. The patient is placed in left lateral decubitus position, and a right poster lateral thoracotomy is performed. The azygos vein is ligated and divided and the posterior membranous walls of the thoracic trachea and mainstem bronchi are exposed. The right vagus nerve is dissected
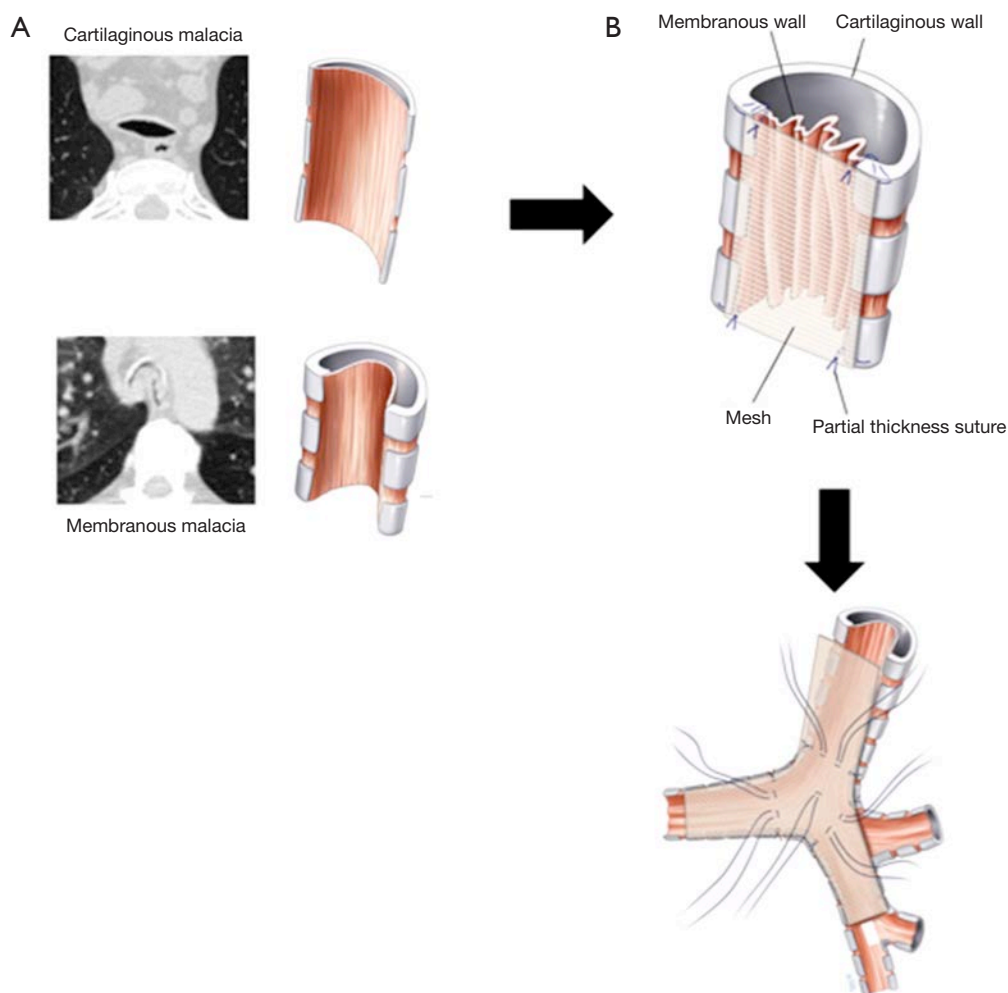
Figure 3 Schematic of expiratory central airway collapse (ECAC). (A) Top: airway represents the form of tracheobronchomalacia (TBM) characterized by weakness that affects primarily the anterior tracheobronchial wall. A representative cross sectional CT image accompanies the diagram. Bottom: diagram represents the form of TBM characterized by invagination of the atrophic posterior membrane into airway lumen. A representative cross sectional computed tomography (CT) image accompanies the diagram; (B) tracheobronchoplasty. Suture is seen passed in a partial thickness mattress fashion through the airway wall. Typically, the entire thoracic trachea is splinted, then the right mainstem and bronchus intermedius, and then left mainstem bronchus [Reprinted with permission (28)].

free and preserved. Care is taken not to entrap the nerve with the mesh or sutures once the posterior plication is begun. The posterior membrane of the trachea is dissected free of any adventitial attachments all the way to the edge of the cartilaginous-membranous junctions bilaterally. To prevent ischemia, aggressive dissection past these junctions anteriorly onto the lateral walls of the trachea is avoided. The transverse airway diameter is measured posteriorly at the proximal and distal trachea, right main stem bronchus, bronchus intermedius, and left main

stem bronchus. A 2×12-inch knitted polypropylene mesh (Ref Number 0112670; C. R. Bard, Inc., Murray Hill, NJ, USA) is fashioned into a Y-shaped posterior splint based on these measurements. A 0.5-cm margin is left on the edge of the Y-shaped mesh to allow a secure, unfrayed material through which to suture. The mesh is then secured using rows of four partial thickness interrupted sutures 4-0 Prolene (Ethicon, Johnson & Johnson, Gateway; Cincinnati, OH, USA) across the width of the trachea from the mesh strip to the tracheal wall. Typically, the entire thoracic trachea is

Table 1 Preoperative and postoperative outcome measures in a cohort of 63 patients from 2002–2009 after tracheobronchoplasty at BIDMC

Metric	N	Preoperative	Postoperative	P value
Six-minute walk test (feet)	33	987±502	1,187±347	<0.005
Karnofsky performance scale	33	62±12	76±14	<0.001
ATS dyspnea score	34	3.06±0.9	1.65±1.01	<0.001
SGRQ quality of life measure	35	74±13	46±21	<0.001
Six-minute walk test (feet)	33	987±502	1,187±347	<0.005
FEV$_1$	37	1.62±0.76	1.66±0.67	0.29

Data shown as means ± SD. ATS, American Thoracic Society; SGRQ, St. george respiratory questionnaire; FEV$_1$, forced expiratory volume in 1 second; BIDMC, Beth Israel Deaconess Medical Center.

splinted first, followed by the right mainstem and bronchus intermedius, and finally the left mainstem bronchus. In our experience, it is not sufficient simply to use the sutures to affix the mesh to the posterior membrane. The mesh is inherently 'floppy', so adding it as a simple reinforcement layer to the malacic airway does not yield the optimal amount of stabilization. Rather, careful selection of the configuration of the individual sutures helps create tension across the airway by keeping the mesh very taut. This process requires row to row adjustments of the sutures, keeping a balance between creating tension and excessively narrowing the airway. Once the posterior splinting is completed, the pleural space is irrigated, and a chest drain is placed. After placement, the endobronchial tube is pulled back into the trachea and flexible bronchoscopy through the tube is performed to assure that an acceptable anatomy has resulted from the tracheobronchoplasty. Occasionally, bronchoscopy can be utilized during suture placement to optimize tension and surveil for full-thickness sutures. After closure of the thoracotomy, the patient is reintubated with a larger single-lumen endotracheal tube to allow aspiration bronchoscopy before extubation.

We have previously reported our experience with a cohort of 218 patients referred for evaluation at BIDMC from 2002 to 2009 (21). Of these, 161 patients were diagnosed by dynamic airway CT and bronchoscopy with severe, diffuse TBM and underwent stenting trial. On follow-up, 99 of these stented patients had amelioration of their symptoms, and 63 underwent tracheobronchoplasty. There were 28 women (44%) in the cohort, and the mean age was 59 years (SD±12.5; range, 35–82 years). Preoperative comorbidities included respiratory conditions, such as chronic obstructive pulmonary disease (37%), asthma (23%),

and Mounier-Kuhn syndrome (8%). Notably, GERD was comorbidity present in 48% of patients. The operation time averaged 373 minutes (SD±93; range, 180–635 minutes). The median hospital length of stay was 8 days (range, 4–92 days), and the median length of intensive care unit stay was 3 days (range, 0–91 days). Complications were seen in 38% of patients, including two deaths (3.2%), both during our original 2002-2005 cohort experience. One patient succumbed to acute worsening usual interstitial pneumonia and the other to a massive pulmonary embolism. Postoperative morbidity included new postoperative respiratory infection in 14 patients (22%), atrial arrhythmia in 6 (10%), acute renal failure (creatinine >2) in 4 (6%), unplanned return to the intensive care unit in 3 (5%), urinary tract infection in 2 (3%), pulmonary embolism in 2 (3%), myocardial infarction and cardiomyopathy in 1 patient (2%), and wound infection in 1 (2%). Reintubation was necessary in 6 patients (10%). A tracheotomy was placed in 9 patients (14%), including four tracheotomies performed intraoperatively immediately after the tracheobronchoplasty was completed in anticipation of the need for frequent aspiration bronchoscopy and tracheal suctioning. Of these patients, five were decannulated successfully. One patient still had his tracheotomy at the 3-month postoperative visit and was subsequently lost to follow up; one patient was lost to follow-up immediately after his TBP. The two patients who died postoperatively both died with tracheotomies in place. Neither reintubation nor tracheotomy was required in the latter half of the series. There were no reoperations for bleeding. Aspiration bronchoscopy was used frequently in the postoperative period (16,25,30).

Surgical stabilization of the malacic tracheal and bronchial airway has yielded significant improvements in

respiratory-related quality of life (St George Respiratory questionnaire), dyspnea indices [Baseline/transition dyspnea index, American Thoracic Society (ATS) Dyspnea Score], performance status (Karnofsky score), and exercise tolerance (6-minute walk test) *Table 1*. Furthermore, central airway stabilization has shown a significant reduction in the mean percentage of expiratory tracheal collapse in malacic airways following tracheobronchoplasty (3,22). Although it is possible to show anatomic improvement central airway collapsibility on dynamic bronchoscopy and CT scan, enhancement of "end organ" effects, such as decreased air trapping have not been demonstrated (3,21). It is uncertain whether the lack of change in air trapping in our entire cohort is due to chronic, irreversible small airways disease from recurrent infections or comorbid conditions (e.g., COPD, asthma), or if a longer time period of follow-up is necessary to document changes.

Surveillance and long-term outcomes

Two distinct considerations should be taken into account when planning patient care following tracheobronchoplasty. First, adequate surveillance should be ensured to manage the long-term complications related to TBP itself. This should include a multidisciplinary collaborative effort including experienced thoracic surgeons, interventional pulmonologists, otorhinolaryngologists and gastroenterologists. Second, a surveillance program should be considered to detect recurrences of symptoms and/progression of disease to cervical trachea or lobar bronchi early enough to allow potentially curative retreatment. At BIDMC, we follow patients post operatively with routine dynamic bronchoscopy and CT surveillance starting at 3 months post operatively to establish a new baseline and then yearly thereafter. In addition respiratory-related quality of life, performance status, and exercise tolerance are measured at these intervals.

Although the long-term morbidity and durability of TBP needs further study, our group has made several recent observations on long-term outcomes. Improvement of symptoms was reported in 77.8% (n=90) at 3 months, 75% (n=56) at 1 year, 67.6% (n=37) at 2 years and 65% (n=20) at 5 years. Airway patency was documented at follow-up dynamic bronchoscopy in 94.6 % (n=90) at 3 months, 85.7% (n=56) at 1 year, 91.4% (n=35) at 2 years and 100% (n=19) at 5 years. Long-term complications have included chronic pain (17%), recurrence of disease requiring redo TBP (8%), dysphagia (9%), and mesh erosion (3%) (31).

Additional treatment and novel therapies

Airway oscillatory devices (flutter valve) or external percussion vests used twice or three times per day can serve as an adjunct for airway clearing therapy. Pneumatic splinting using nasal continuous positive airway pressure (CPAP) has been described as an alternative therapy with variable success; yet, it requires an external device difficult to use with daily activities (32). Robotically assisted bilateral bronchoplasty, bioresorbable three-dimensional airway stents, endobronchial laser therapy, and tracheal cartilage regeneration techniques are under investigation and further studies are warranted to determine their safety and efficacy (33-35).

Conclusions

Severe, diffuse TBM and EDAC in the adult population are conditions that affect the central airways and often result in dyspnea, intractable cough, inability to clear secretions, and recurrent infections. Initial evaluation is done with dynamic bronchoscopy and CT scanning. Pulmonary function tests are not diagnostic but help to stratify patients during the initial evaluation. Once severe (>90%) collapse of the airways is observed, further investigations are required to determine if airway stabilization will improve symptoms. Short-term airway stabilization with tracheobronchial stenting in patients with severe symptomatic TBM serves as a surrogate for the effects of surgery, though frequent side effects and complications unique to the stent trial may be seen. Surgical stabilization of the central malacic airways by posterior splinting with a prosthetic mesh (tracheobronchoplasty) results in significant symptomatology improvement, health-related quality of life, as well as functional and exercise capacity in carefully selected patients. Long-term anatomical improvement may be achieved, but close surveillance is necessary to detect recurrence or progression of malacia. As our experience with the treatment of TBM increases, we hope to refine the assessment tools that will help us understand which patients truly benefit from this highly technical operation. Close coordination of a multidisciplinary team of dedicated radiologists, interventional pulmonologists, and thoracic surgeons helps ensure optimal selection and treatment of these challenging patients.

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Footnote

Conflicts of Interest: The authors have no conflict of interest to declare.

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Tracheal and bronchial tumors

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Abstract: Although primary tracheobronchial tumors are extremely rare in children, recurrent respiratory symptoms resistant to conventional therapy require further investigations to exclude possible malignant obstructive causes. As the matter of fact, early diagnosis may allow minimally invasive surgeries, improving the standard of living and the globally survival rate. The aim of this article is to provide an overview of diagnosis and management of tracheobronchial tumors in the early age, since only few reports are reported in the worldwide literature.

Keywords: Primary tracheobronchial tumors; pediatric tumors; subglottic hemangioma; fibro-bronchoscopy; sleeve resection

Introduction

Tracheobronchial tumors are extremely rare in the paediatric population, accounting for 0.2% of all cancers in this range of age (1). They include both benign and malign lesions (*Table 1*). In the former group, the most common histological entities are represented by infantile hemangioma and squamous papilloma, while inflammatory pseudotumors, leiomyomas, granular cell tumor, juvenile xanthogranuloma, tracheal lipoblastoma and laryngotracheal chondromas occur more sporadically. The latter group includes carcinoids, mucoepidermoid carcinomas and less frequently rhabdomyosarcoma, leiomyosarcoma and adenoid cystic carcinoma (2,3). Because of their low prevalence in the paediatric age and the absence of specific signs and symptoms, primary tracheobronchial tumors are often not suspected or misdiagnosed. This inevitably leads to delayed definitive diagnosis and treatment (4). In the worldwide literature, relative little attention has been provided to their management and only few studies are reported. The aim of this article is to review the current literature, producing a complete overview with regards to their pathological and clinical features, requirement of diagnostic imaging, surgical treatments and follow up.

Pathologic classification and tumoral behavior

Primary tracheobronchial tumors include a broad spectrum of pathologic entities arising from the respiratory epithelium, the salivary glands or the mesenchymal tissue of the tracheobronchial tree. In literature great confusion exists about their real prevalence. Several studies report a clear predominance of the malignant forms (65% of cases, approximately) but infantile hemangioma and papilloma are often excluded in these epidemiological analyses (3,5,6).

Table 1 Primary endobronchial tumors in children

Benign
Hemangioma
Papilloma
Inflammatory pseudotumors
Leiomyomas
Mucus gland tumors
Granular cell tumor
Juvenile xanthogranuloma
Lipoblastoma
Chondromas
Malignant
Carcinoid
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Rhabdomyosarcoma
Leiomyosarcoma

Malignant tumors

In these forms, the survival rate is mainly influenced by histological type, lymph node involvement and by the type of surgery (7).

Bronchial carcinoid and mucoepidermoid carcinoma are the most common histopathological type, with a good prognosis overall. The former accounts for 80% of all malignant forms. It arises from the neuroendocrine cells of the respiratory epithelium, mainly from the lobar bronchi of the right side (75% of case, approximately). Basing on the mitotic activity rate and on the grade of tumour necrosis, they are usually classified as typical and atypical, with the latter one showing a more aggressive behaviour and a worse prognosis. Lymph nodes metastases are frequently described, while local recurrences and distant metastasis rarely occurred (2).

Mucoepidermoid carcinoma appears as an exophytic mass originating from the submucosal bronchial glands of the tracheobronchial tree. They are classified into low, intermediate and high grade tumors, in relation to cell type and pleomorphism, mitotic index and the presence of cystic structures. The most common in children is the low-grade type which is primarily composed of mucous cells (4).

Rhabdomyosarcoma and leiomyosarcoma along with adenoid cystic carcinoma are the less frequent malignant form reported in the paediatric population. The former accounts for 5.8% of all paediatric endobronchial tumors (8) with previous radiation therapy, genetic predisposition and immunological factors as main documented risk factors for its occurrence (9). Leiomyosarcoma is even more sporadic, making up 3.8% of all paediatric forms (8). Adenoid cystic carcinoma shows an aggressive attitude, with local relapse and local lymph nodes metastases (10) but it is infrequently described in children.

Benign tumors

In children infantile hemangioma is a relatively frequent and well-known airway tumour. It consists of a vascular proliferation of packed endothelial cells with a lobular architecture. It typically look like as localized, smooth, compressible mass arising from the subglottic area, but sometimes it could be diffuse without any mucosal elevation (3). Because of its localization, it may become potentially life-threatening especially during the proliferative phase of its growth. Conversely to congenital hemangioma and other vascular anomalies, the immunohistochemical staining for glucose transporter-1 protein (GLUT-1) is usually positive in the endothelial cells (11).

Granular cell tumours are soft tissue neoplasms probably derived from Schwann cells. Approximately half of all cases originates in the head and neck, with 10% of these one having a laryngeal involvement (12,13). In children, surgical resection should be considered because of recurrent obstructive symptoms, although malignant transformation has never been documented (14).

Inflammatory myofibroblastic tumor, also known as inflammatory pseudotumor, consists of a variable mixture of myofibroblastic mesenchymal spindle cells accompanied by inflammatory cells and collagen. Found most frequently in upper trachea it could occur anywhere else. Metastases are occasionally referred (15).

Usual manifestations of the juvenile xanthogranuloma are cutaneous lesions appearing in the first year of life. Airway involvement is rarely described but it can result in severe respiratory obstruction. Since most of them regress spontaneously, endoscopic or surgical excision is required only in case of involvement of vital structures (3).

In addiction also laryngotracheal chondromas and tracheal lipoblastoma are reported although their appearance in children is extremely rare (16).

Sign and symptoms

Sign and symptoms depend on tumor histology and localization. In case of involvement of the upper respiratory tract, when more than 50% of the lumen is interested, obstructive symptoms such as stridor, wheezing and dyspnoea appear. Furthermore patients frequently experience chronic cough due to persistent mucosal irritation or inadequate clearance of distal airway secretions (5). Depending on the degree of the lumen obstruction, bronchiectasis and pulmonary atelectasis could appear, leading to chronic pneumonia (5). Haemoptysis could also appear as consequence of mucosal ulceration and bleeding (14). In relation to each histological type, the lack of pathognomonic symptoms lead to frequent misdiagnoses with other conditions (such as bronchitis, pneumonia or asthma) causing diagnostic delayed (2). Consequences are cancer spreading and metastases with permanent pulmonary damage following radical surgery (2). Actually, fewer than 10% of patients with bronchial carcinoid develops the typical syndrome characterized by hypotension, diarrhea and flushing (17,18). The more insidious and life-threatening neoplastic growth of the upper airway is the hemangiomatous proliferation. Subglottic involvement may be asymptomatic at birth, but later in life inspiratory stridor usually occurs, especially during feeding or crying. Since these symptoms are often intermittent, they could be easily misdiagnosed as protracted laryngotracheitis or recurrent croup, even without fever. For these reason, children younger than 6 months with biphasic stridor should be evaluated with nasopharyngolaryngoscopy or rigid bronchoscopy (19). Persistent respiratory tract infections are also common. Regarding mediastinal infantile hemangioma, it can also occur as an extension from the primitive site, adding an extrinsic compression to the airway (2).

Imaging and endoscopic assessment

Because of the not-specific presenting respiratory symptoms, patient evaluation usually begins with a chest X-ray. Although it is not diagnostic in most cases, it usually shows indirect signs of bronchial obstruction (such as segmental atelectasis, bronchial dilatation or distal air trapping) which compel further evaluations. The evidence of persistent infiltrate advocate chest CT scan or bronchoscopy in order to distinguish between congenital lung defects, external compression of the airways, intraluminal foreign bodies or endobronchial masses (4). Actually the gold standard for primary tracheobronchial tumors detection is CT scan with intravenous contrast administration. Although the high radiation exposure, it is a fast diagnostic technique with great spatial resolution that allows the clear identification of primary tumor site and extension, the anatomic relation with adjacent organ and vessels and the presence of synchronous lesions distally to primary obstructive site (3). Magnetic resonance is useful for staging malignancies and detecting distant spread without exposing the body to ionizing radiation (20).

Bronchial carcinoids are usually described as well-defined exophytic masses which could entirely occupy the airway lumen causing obstructive symptoms. Full thick involvement of the bronchial wall and extraluminal extension are also possible. They tend to be highly vascularized, showing homogenous contrast enhancement on the CT scan images. Different patterns of calcification are described in 30% of cases (3). Cells expression of somatostatin receptors is a distinctive feature of carcinoid tumors so that radiolabeled somatostatin analogues are usually used in scintigraphy as complementary study for diagnosis and follow up (6). Mucoepidermoid carcinomas appear as intraluminal slow-growing vascular polypoid masses with a high rate of calcifications (50% of cases) (6).

Infantile hemangioma shows different features on CT scan images in relation to their phases. During the proliferative growth it appears as a uniform enhancing soft-tissue mass while during the involution phase the contrast enhancement varies due to its fibrofatty infiltration (3). In any case, endoscopy with biopsy remains crucial for definitive diagnosis based on histological type (21). Both flexible endoscopy and rigid bronchoscopy are used to explore the lumen of the airway, in order to identify tumor location and get tissue samples (22,23). Operative maneuvers such as hemostasis, tumor debulking or airway stenting can also be provided (23).

Treatment

Removing the lesion with great spare of the functional parenchyma is the goal of the surgical treatment. Although several reports referees about endoscopic resection of tracheobronchial tumors, this approach remains controversial in favour to radical surgery (22-24). Conversely, the mainstay of the therapy of infantile hemangioma is medical. Literature supports the prompt initiation of propranolol, which should be continued until the involution phase, which usually occurs at the end of the first year (25).

Endoscopic treatment

Endoscopic treatments are used to ablate endobronchial tumors. In 2013, Sjogren and colleagues published the largest series of endoscopic treatments of tracheobronchial using the carbon dioxide laser. Although the first results were encouraging, several limitations were identified and different surgical complications were highlighted: bleeding, transmural injuries, fibers ruptures and dislocations. Repeated endoscopic treatments were required to remove completely the neoplastic mass exposing each patient to several anesthesiological procedures (24,26,27).

Jaramillo and colleagues reported that endoscopic treatment of mucoepidermoid carcinoma makes really arduous their complete excision, preventing lymph node staging (4). Endoscopic treatment of bronchial carcinoid was also controversial: guidelines considered it only in selected patients with typical carcinoid localized proximal to subsegmental level with polypoid growth and no signs of bronchial wall infiltration or lymph node involvement (6).

As mentioned above, endoscopy has a few utilities in the treatment of infantile hemangioma, which use is limited to the evaluation of the pharmacological response. Laser ablation is a second line therapy in oreder to allow an adequate airway lumen. However circumferential coagulation must be avoided because of the risk of subglottic stenosis due to scar formation (19).

Surgical treatment

Aim of surgical treatment is complete tumor resection. In order to prevent later functional limitations, normal lung tissue must be spared as much as possible. Although pneumonectomies and lobectomies have been typically performed for bronchial tumours, parenchyma-saving procedures, such as sleeve resections and bronchoplasties, are the main procedures performed recently (28). Bronchial carcinoid and mucoepidermoid carcinoma are reported to metastasize to the lymph nodes so that their biopsy is strictly recommended (14,24,29).

Preventive tracheotomy is not usually recommended. Also in case of in case of infantile hemangioma, tracheostomy, which was commonly used in the past, is not required now. It should be performed in selected cases of severe tracheal obstructive symptoms, however it should be avoided when primary resection of the tumor or biopsy with endoscopic debulking could be possible (14).

In case of lesions located in the laryngeal tract an anterior transverse collar incision is indicated. During surgery a temporary intra-operative tracheotomy could be useful in order to remove the tracheal tube. After dissection of the subcutaneous tissue and the platysma muscle, the infrahyoid muscles and the thyroid isthmus are retracted in order to obtain free access to the airway. A laryngofissure may help to reach the site of the lesion, depending on its localization. Radical tumorectomy can be safely performed, if there is no infiltration of the cartilaginous tissue with clear cleavage planes. Partial resection is mandatory in case of larynx infiltration. Laryngotracheal defect can be repaired by rib graft (30). Huge neoplastic masses required cricotracheal resection with an end-to-end anastomosis. Extubation is usually carried out at the end of surgery, except for selected cases (14). Postoperative complications such graft infection or collapse, excessive proliferation of the granulation tissue, extensive malacia, vocal fold palsy or laryngotracheal stenosis could occur rarely (14).

Neoplastic lesion involving the upper trachea can be approached by transverse cervical incision, while sternotomy is usually not required. Flexible intraoperative bronchoscopy is performed to identify the tumor site. The neoplastic mass is then removed through a tracheal window or a cylindrical resection. In the latter case an end-to-end tension free anastomosis is advocated. Lymph nodes biopsy is mandatory (7).

Conversely, when the tumor is identified in the inferior part of the trachea, a sternotomy is usually required. Each surgical approach must be individualized depending on the tumor site and extension (31).

In case of masses localized in the main bronchi, with proximal and distal stumps free from neoplastic lesions proved by frozen sections, the gold standard is the sleeve resection. It consists of the segmental removal of the affected bronchi and the anastomosis of the two bronchial stumps. Intra-operative bronchoscopy and endobronchial ultrasound may help to guide the appropriate bronchial resection. Entire preservation of health lung parenchyma is the clear advantage of this approach (27,32).

Although for congenital pulmonary malformation thoracoscopic lobectomy and segmentectomy are now generally accepted (33), the same procedures for tracheobronchial tumors have not been attempted in the pediatric population yet (34,35).

Medical treatment

Given the benign course of the most common tumours

when radical resection is achieved, conservative treatment is not usually performed (36). Conversely, regarding the management of tumour relapses, both chemotherapy and radiation therapy are required (14).

Follow up

Pediatric oncological guidelines are lacking and no recommendations exist on medical, radiological and endoscopical follow-up. Primary surveillance should identify the related symptoms of neoplastic relapses. Al-Qahtani and colleagues propose clinical examination and chest X-ray every 3 months for the first year and every 6 months thereafter. Carcinoid tumors required abdominal ultrasound, chest computer tomography and urine and serum 5-HIAA every 6 months to exclude metastases. Bronchoscopy should be performed every 6 months for the first year and then yearly, especially in case of partial surgical resection (37).

Conclusions

Tracheobronchial tumours usually are not suspected in children experiencing recurrent respiratory symptoms. This is often cause of delayed diagnosis. Conversely, respiratory symptoms resistant to pharmacological treatment should deserve further investigations to early identify possible obstructive causes. Early diagnosis may allow to perform parenchyma-saving surgeries, avoiding the functional problems related to extensive lung resection.

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Footnote

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Central airway tumors: interventional bronchoscopy in diagnosis and management

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Abstract: The diagnosis of central airway tumors is usually challenging because of the vague presentations. Advances in visualization technology in bronchoscopy aid early detection of bronchial lesion. Cryotechnology has great impact on endobronchial lesion sampling and provides better diagnostic yield. Airway tumor involvements result in significant alteration in life quality and lead to poor life expectancy. Timely and efficiently use ablation techniques by heat or cold energy provide symptoms relief for central airway obstruction. Prostheses implantation is effective in maintaining airway patency after ablative procedure or external compression. Combined interventional bronchoscopy modalities and other adjunctive therapies have improvement in quality of life and further benefit in survival. This review aims to provide a diagnostic approach to central airway tumors and an overview of currently available techniques of interventional bronchoscopy in managing symptomatic central airway obstruction.

Keywords: Central airway obstruction; bronchoscopy; intervention; ablative technologies; stents

Introduction

Patients with central airway tumors usually have nonspecific clinical manifestation and lead to delayed diagnosis. Computed tomography (CT) scan is the best noninvasive method for airway lesion evaluation (1). Bronchoscopy is still the mainstay to approaching endobronchial lesion. The conventional methods to obtained specimen include forceps biopsy, brushing or washing the lesion under direct vision. However, the diagnostic yield of conventional forceps biopsy is limited because of the small size of tissue sample and crush artifacts (2,3). Newly developed cryotechnology provide larger sample than that of conventional forceps biopsy and have better diagnostic yield (2).

Dyspnea is the major symptoms in patients with central

airway obstruction which limit the daily activity of patients. Unfortunately, not only 20% to 30% patients with primary lung cancer experience this suffering symptoms, 2% patients with solid tumors also have endobronchial metastasis which may postpone their anti-cancer therapy because of severe dyspnea (4,5). In recent decades, interventional bronchoscopy has being an effective treatment modality for central airway obstruction (6-8). In patients with limited performance status due to central airway obstruction, the functional status will improved after interventional bronchoscopy and have the chance to receive chemotherapy (9,10). The exercise capacity, lung function and quality of life are improved after therapeutic bronchoscopy (11). Moreover, the survival may also been prolonged after airway stenting in selective situation (12,13).
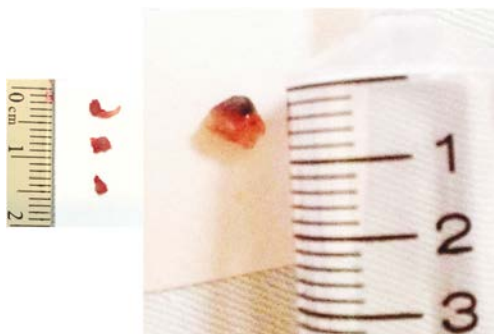
Figure 1 Specimens comparison between traditional forceps biopsy (left) and cryotechnology (right).

Intraluminal   Extraluminal   Mixed

Figure 2 Types of central airway obstruction.

Here, we provide a clinical review of interventional bronchoscopy in diagnoses and management of central airway tumors.

Diagnostic modalities

Computed tomography

Only less than 30% patients with tracheal tumors have been diagnosed via chest radiography (14). Traditional CT scan is more sensitive and can provide information on the extent of airway lesions. Newly developed multidetector CT (MDCT) can accurately detect airway tumor locations, natures, quantities (1). The extra luminal anatomy is also clearly depicted. Thus, MDCT is a rapid and non-invasive method to provide comprehensive information about the extent of disease process before surgery or interventional bronchoscopy (1).

Visualization of bronchoscopy

Bronchoscopy is the mainstay to approaching endobronchial lesion under direct vision. In addition to conventionally white light bronchoscopy, autofluorescence (AFB) and narrow band imaging (NBI) are new visualization techniques of bronchoscopy which can aid detection of

bronchial mucosa lesions (15). Although the specificity of AFB is low and similar to white light bronchoscopy, there is no doubt in usefulness of detecting early bronchial mucosal lesion and evaluate the margin of mucosal involvement (16,17). NBI is designed to detect angiogenesis and neovascular lesion. The diagnostic accuracy is increased under NBI bronchoscopy (15). Both of them have superior sensitivity comparing with white light bronchoscopy [3-5]. Endobronchial ultrasonography (EBUS) is also helpful in evaluating the extent of airway lesion involvement (14,18).

Tissue sampling: forceps versus cryotechnology

Forceps biopsy under direct bronchoscopic vision is the most common method to obtain tissue sample from endobronchial lesion. However, the size of tissue sample is limited by the forceps size. Small samples with crush artifacts are probably insufficient for accurate diagnosis. The diagnostic yield is only 85% of conventional forceps biopsy and patients usually have to repeat bronchoscopy (2,3).

Cryotechnology has been used as a therapy for central airway obstruction and hemoptysis (19). The samples from cryotechnology are larger than conventional forceps biopsy and have better diagnostic yield (95% to 100%) (3,20,21) (*Figure 1*). Besides, the tissue architecture will not be damaged by cryotechnology and thus facilitate histological analysis (22). Tumor bleeding is a major concern after biopsy. Theoretically, vasoconstriction and capillary microthrombosis after cryotechnology may ameliorate bleeding (20,23). Hetzel *et al.* (3) reported a greater incidence of mild bleeding after cryobiopsy. However, the rate of severe bleeding is comparable of forceps biopsy and cryobiopsy. In recently published, prospective study, two cryo biopsies was found to be optimal for diagnosis and greater than three bryobiopsies will increase the risk of bleeding (24). Cryotechnology has been a considerable choice for endobronchial lesion biopsy with better diagnostic yield and minimal complication.

Management

There are three types of central airway tumor involvement: endoluminal (tumor within airway), extraluminal (airway narrowing from external compression), and mixed (6) (*Figure 2*). A variety of techniques in endoluminal tumor debulking has been developed and has been shown to be effective in reliving symptoms (22). In addition to extraluminal and mixed type central tumor involvement,

Table 1 Types of central airway obstruction and treatment modalities

	Intraluminal	Extraluminal	Mixed
Mechanical debulking	+	–	+
Electrocautery	++	–	+
Argon plasma coagulation	++	–	+
Laser	++	–	++
Cryotherapy	+++	–	+++
Stent		+++	++

–, not recommended; +, weakly recommended; ++, recommended, +++, strongly recommended.

airway stenting is also useful in preventing recurrence and restore the airway patency after intraluminal tumor debulking (25). The choice of techniques depends on the characteristics of stenosis, the condition of patient, available techniques and the operator's expertise (*Table 1*).

Rigid bronchoscopy and mechanical debulking

Rigid bronchoscopy is a traditional procedure, which have been introduced under general anesthesia (26). Contraindications of rigid bronchoscopy include cervical spine instability, facial trauma, laryngeal obstruction (27). The easy airway security and large working space provide more space for interventional procedure processing. However, in patients with severe airway obstruction and respiratory failure will experience great risk of general anesthesia because of high oxygen demand and illness severity (28).

Recently, Vishwanath *et al.* (29) reported their 30-cases experience of solely mechanical debulking under rigid bronchoscopy in managing central airway tumors. The successful rate reached 82.6%, however, the complication rate is as high as 32.3% with significant bleeding in 25.8% patients. Although they suggested that mechanical debulking under rigid bronchoscopy was probably quicker than thermal ablative therapy, there was no direct comparison of procedure time between difference methods. Combining mechanical debulking with a complementary thermal ablative procedure may be a safer choice in bleeding control (25).

Electrocautery

Electrocautery used high-frequency electric current

to cause heating which lead to coagulation or tissue vaporization (30). It can be delivered via rigid or flexible bronchoscopy. The effects depend on the power setting, surface area, electrical properties of tissue and the contact time (22). In one large retrospective series of electrocautery for airway obstruction, the luminal improvement was achieved in 78% patients with 6.8% complication rate (31). Electrocautery provided equally effective and constant palliation in patients with airway obstruction as that provided by neodymiumdoped:yttrium-aluminum-garnet (Nd:YAG) laser therapy. However, the cost of electrocautery is significant lower than Nd:YAG laser (32). Thus, electrocautery is a more accessible modality worldwide.

The complications include damage of underlying cartilage which may lead to airway stenosis, bleeding, perforation, pneumothorax, malfunction of pacemaker (22). Besides, airway fire is also a major concern in the presence of high oxygen concentration and flammable substance (such as silicone stent or endotracheal tube). Above complications could be ameliorated after restricting the fractional inspired oxygen less than 40% and the limiting the power output do not exceed 30W (30).

Argon plasma coagulation (APC)

APC is a non-contact method of electrocautery and can be introduced via both rigid and flexible bronchoscopy (33). The noncontact feature of APC allows extent and rapid coagulation, but the depth of penetration is more superficial (2–3 mm) and limited by increased tissue resistance after coagulation and desiccation (33,34). The major applications of APC are hemostasis and tissue destruction and particular effective in vascular lesion (35). Besides, APC is an effective therapy for airway obstruction secondary to endobronchial lesion (36). Not only significant endobronchial tumor reduction, clinical dyspnea score and forced expiratory volume in one second (FEV1) are also improved after procedure (37). Because of the superficial effect and superiority in hemostasis, APC is usually used as a part of multi-modality approach for tumor debulking (33).

The complication rate of APC is approximately 2% (30). The most severe fatal complication is intracardiac gas embolism and cerebral embolism (38,39). Above conditions may be minimized by keeping the flow to less than 0.8 L/min and maintaining a safe distance of 2–5 mm (34).

Laser

Laser therapy is a widely used ablative technique for tumor

debulking which can be performed using flexible or rigid bronchoscopy with different gases (22). Neodymium: yttrium-aluminum-garnet (Nd-YAG) laser is the most frequent used (34). The most common indication is relieving central airway obstruction. It is particular effective for intraluminal and mixed type airway obstruction and less suitable for extraluminal compression (40). In additional to constant and immediate effect in tumor shrinkage, the quality of life and overall health are also improved significantly in patients with malignant central airway obstruction due to lung cancer (41). Although laser monotherapy is quite effective in alleviating symptoms from malignant central airway obstruction, survival benefit will be improved when it combined with multimodal adjuvant therapy (including brachytherapy, chemotherapy, radiotherapy, stenting, chemoradiotherapy) (42). However, the high cost of laser therapy is a disadvantage of the usefulness worldwide and can be alternated with electrocautery, APC or cryotherapy (32,40).

The complications of laser therapy is around 8%, including hemorrhage, endobronchial fire, pneumothorax, and air embolism (40). The periprocedural death is 1–3% (30). Because of the inability to visualizing penetration depth, perforation of major vessel will lead to fatal hemoptysis. This can be avoided by limiting the power less than 40W (34,40). Endobronchial fire can be prevented by restricting the fractional inspired oxygen less than 40%. Besides, patients who were over 60 years of age, with arterial hypertension or chronic obstructive pulmonary disease were associated with higher complication rate (43). Thus, in additional to the modification in setting, the patient selection is also important to minimizing complications.

Cryotherapy

Cryotherapy uses extremely cold (–70 ℃) to tissue and causes tissue necrosis with repeated freezing and thawing cycle (30). It can be introduced with rigid or flexible bronchoscopy. The effect of cryotherapy is usually delayed but prolonged, with capillary microthrombi formation (25). The efficacy depends on the cooling rate, the minimum temperature reached, the cycle of freezing and thaw (22). Unlike thermal ablative therapy (electrocautery, laser, APC), cryotherapy has no risk in airway fire and will not lead to tissue edema after procedure (23). Because of low water content of cartilage, collagen and poorly vascularized tissue, cryotherapy has very small effects on them. As such, the scarring is minimal and the damage of cartilage is few (23).

Cryotherapy is mainly indicated for a palliative treatment for intraluminal airway obstruction and not recommended in submucosal lesion or extraluminal compression (34). The overall success rate of significant recanalization exceeds 80% in one systematic review (44). In additional to improvement in dyspnea, cough, and hemoptysis, the lung function, performance status are also improved after cryotherapy (19). When combined with systemic chemotherapy and/or radiation, the survival benefit is significant (9,45). As the effect of cryotherapy is delayed, it is usually not suitable for patients with impending respiratory failure secondary to airway obstruction. Use the principle of cryoadhesion, cryosurgery has been performed with rapid relief of tumor obstruction. However, additional modalities, such as APC, are required to achieve hemostasis (34). Recently, Boujaoude *et al.* reported one case with acute central airway obstruction has been managed successfully with cryosurgery alone using "freeze and pull" technique. Although the experience is few, however, it provides the opportunity for patients with emergent airway obstruction under high oxygen requirement to liberating from mechanical ventilation (46).

The complication rate is low (0–11%), most of them were minor and easily manageable (44). The risk of perforation and airway fire are non-existent, since the cartilage is cryoresistant. Thus, cryotherapy is safe while the inflammable substance nearby the obstructive lesion (*Figure 3*).

Stent

The endobronchial stent is the main choice to alleviate extraluminal airway compression and is also available to relieve intraluminal and mixed type central airway obstruction when combining with other endobronchial therapies (25). Airway stent is usually a palliative treatment for malignancy. It provides a bridge for airway patency in patients undergoing systemic chemotherapy or radiation. Although the overall survival was not changed, the median survival time could be increased after airway stenting if it was combined with adjuvant therapy (47).

Theoretically, the ideal stent should be strength enough, not migrate, easy to insert and remove, flexible enough to mimic airway physiology, not impair mucociliary clearance, not induce granulation tissue formation, and cost-effective (26). However, it has not been developed.

Before stent implantation, the size, diameter and length have to be chosen according to CT scans and bronchoscopy.
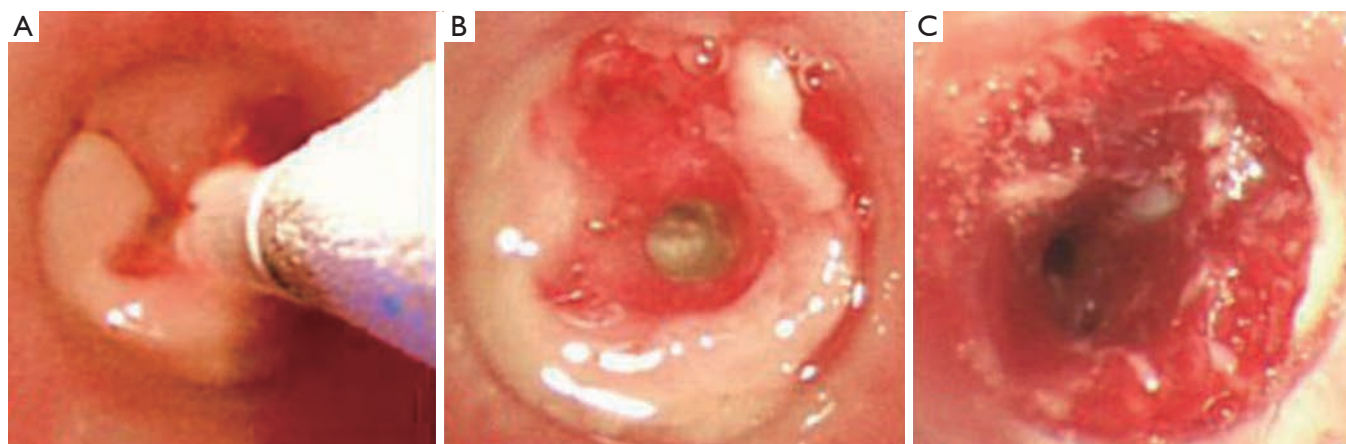
Figure 3 Cryotherapy successfully recannulized airway obstruction secondary to silicone stent induced granulation.

Silicone stents

Silicone stent has to be deployed by rigid bronchoscopy under general anesthesia (30). The most commercially available silicone stents are Dumon stents, which have two main types: straight and bifurcated stents (26). The size, length and diameter are chosen preoperatively and can be adjust by cutting. Because it is easy to insert and remove, with few granulomatous reactions, silicone stent has been recommended as first line treatment and is particular suitable for benign lesion for the longer lifespan (25).

The major drawbacks of silicone stent include the necessity of general anesthesia, higher migration rate, mucus plugging, thicker wall and lead to narrow internal diameter. Mucolytic nebulization is essential to prevent dense secretion and asphyxiation (25).

Self-expandable metallic stents (SEMS)

SEMS is mainly used to treat airway obstruction or tracheoesophageal (TE) fistula due to malignancy (*Figure 4*). Metallic stent is also an alternative choice in benign disease if the patients are poor surgical candidates or the airway is highly tortuous (30,48). SEMS can be introduced via rigid and flexible bronchoscopy. There are partial covered, fully covered and uncovered stent. Covered stent is preferred in malignant lesions and particular suitable for covering TE fistula (49). Uncovered stent is mainly used in highly distorted stenosis. Unlike silicone stent, SEMS provide thinner wall construction, greater airway diameter, better conformation with irregular airway, easier placement and less migration rate. The size of stent should be chosen accurately before procedure. The length of stent has to provide 0.5–1.0 cm overlap at each end of the stenosis.

The diameter of the stent should be 1–2 mm greater than the estimated diameter of the airway (30). Fluoroscopy is usually necessary for SEMS placement. However, it is not available in many intensive care units (ICU) and requires special facilities. Lin *et al.* (28) reported 26 mechanically ventilated patients have been successful inserted metallic stent under flexible bronchoscopy without fluoroscopy guidance. More than half patients have liberated from ventilator successfully.

Metallic stent is effective in reliving symptoms of airway obstruction, facilitating to liberate from ventilator, improving pulmonary function and performance status (50-52). Compared with poor performance status, patients with malignant central airway obstruction under intermediate performance status have survival benefit after airway stenting (12). This suggests that timely airway stenting before morbid complication is quite important.

The complications of SEMS include stent malposition, migration, fracture, mucus impaction, halitosis, bacterial colonization and granulomatous tissue formation. In uncovered and partial covered stent, the re-epithelialization and excessive granulation formation in the edges are the most frequent complications, which cause the difficulty in stent removal (48,53). Benign structure airway obstruction prior to stent implantation is independent factor for granulation tissue formation (54). SMES fracture is of major concern because of the possibility of complete airway obstruction and perforation (55). Pretreatment tortuous airway in 3-dimensional CT scan predicts metallic stent fracture. SEMS implantation in such situation should be cautiously evaluated (55,56). Besides, the complication rate in benign conditions is twice higher than malignant disease

Figure 4 Self-expandable metallic stents (SEMS) implanted successfully for covering tracheoesophageal (TE) fistula in patient who was under mechanical ventilation without fluoroscopy guidance.

(42.2% *vs.* 21.1%) owing to the longer follow-up period and longer lifespan (51). In one largest series of lung transplant recipients, the 5-year survival was significant lower in patients receiving metallic stent insertion. Re-stenosis and airway bacterial colonization are the major problems (52). Because of severe complication after long term SEMS implantation, the US Food and Drug Administration (FDA) have warned that metallic stent is not advised to treat benign disease.

Developing stents
Concerning the granulation tissue formation after airway stenting, drug eluting stent with mitomycin C have been observed to reducing granulomatous reaction and less mucus trapping. In animal studies, cisplatin eluting stent have steadily and sustained released drug up to 4 weeks and helpful to against malignant cells (57).

In benign or reversible cases, the airway stent is usually needed temporary. There are 70% patients with post-intubation or post-tracheostomy tracheal stenosis had been successfully treated by silicone stent implantation after 18 months (58). Thus, the removability of stent is quite important. Biodegradable stent has been designed to maintain airway patency for a predetermined duration. It is a temporary support device until the nature tissue regains its strength and can be removed by cellular activity in a biological environment. There are four human studies until now. Only one adult study showed relative good outcome up to 4 years, the outcomes of the other 3 pediatric studies were not satisfactory and associated with repeat stenting after stent absorption. Besides, the cost of biodegradable

stent is much higher than others. The safety and toxicity are also the major concerns (59).

Symptoms from central airway tumors result in poor quality of life and disaster outcome. The survival would not exceed 1–2 months if the patient untreated. However, in such situation, patients' performance status, pulmonary function and comorbidities are usually limited the possibility of surgery (25). Interventional bronchoscopy provides a less invasive choice with high technical success rate (90–98%) and is effective for central airway obstruction to improve quality of life and survival (10,11,13). The complication is relative rare (3.9%) with few mortality (0.5%) (60). Nevertheless, the benefit is difficult to predict in patients under different situation. Guibert *et al.* (61) conducted a retrospective study involving 204 patients with malignant central airway obstruction. They found that higher American Society of Anesthesiologists (ASA) score, non-squamous histology, metastatic tumors and those who were treatment naïve patients had the worst survival. In one largest, multicenter, prospective study, Ost *et al.* (10) demonstrated that patients with ASA >3, renal failure, primary lung cancer, left mainstem involvement and TE fistula were associated with failure. They also found that the complication rate was higher in those with ASA >3, re-do bronchoscopy, receiving procedure under emergent or urgent situation. Thirty-day mortality was associated with poor performance status and ASA >3 (60). However, the patients with higher baseline Borg score had the greater improvement in dyspnea and quality of life. Since patients at the highest risk may have the greatest benefit, therapeutic bronchoscopy should not be withheld from patients solely based on risk assessment (10).

Conclusions

Newly developed visualization technologies of bronchoscopy provide more rapid, accurate, precise diagnosis of endobronchial lesions. Cryobiopsy is a safe technique with greater diagnostic yield and provides a better specimen quality than traditional forceps biopsy.

Interventional bronchoscopy enables the restoration of airway patency and plays an important role in the treatment and palliation for malignant airway obstruction. Mechanical debulking, electrocautery, APC and laser provide immediately symptoms relieve under urgent situation. Cryotherapy is preferred to use in the selective situation because of the delayed effects. Airway stenting is particular suitable for extraluminal compression and is also effective for intraluminal involvement. Drug eluting and biodegradable stents are developing to reduce the complication after long term implantation. Since more complication and less benefit have been expected in urgent situation, timely interventional bronchoscopy should be prudently considered before morbidity coming. The selection of modalities depends on the patients' condition, disease manifestation, availability of equipment and physicians' expertise.

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Footnote

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Tracheobronchial tumors

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Abstract: Tumors of trachea and bronchi are uncommon and can occur in the form of benign or low- and high-grade malignant tumors. Although tracheobronchial tumors (TBTs) represent only 0.6% of all pulmonary tumors, they are clinically significant. Delays in diagnosis of these tumors commonly occur because the signs and symptoms caused by these tumors are nonspecific and chest radiographs are often considered unremarkable. Therefore, novel radiological techniques and better access to flexible bronchoscopy enable detection of larger number of TBT. The purpose of this article is to provide a review of tracheal and bronchial tumors and discuss significant aspects of the different TBT with focus on clinical manifestations and diagnostic procedures.

Keywords: Trachea; bronchi; tumor; diagnosis

Introduction

Pure tracheobronchial tumors (TBTs) are a rare entity that may present with diverse pathological findings and may challenge in their diagnosis and management. The malignant tumors are more frequent than benign ones. Although TBT tumors represent only 0.6% of all pulmonary tumors, they are clinically significant (1,2). These tumors are often revealed incidentally.

The symptoms of an endobronchial tumor primarily depend on its size rather than pathologic characteristics of the tumor itself. They may be clinically significant, causing airway obstruction and mimicking malignant neoplasms and asthma or chronic obstructive pulmonary disease (COPD) (1-3). Today, novel radiological techniques and better access to flexible bronchoscopy enable detection of larger number of TBT. We present a review of tracheal and bronchial tumors and discuss significant aspects of the different TBT with focus on clinical manifestations and diagnostic procedures.

Diagnosis

In the early stages, both benign and malignant endobronchial tumors may have similar signs and symptoms which can be misdiagnosed as an asthma, COPD or pulmonary infection. Most commonly, the patients seek treatment because of cough and hemoptysis, chest pain, dyspnea, localized wheezing, recurrent pneumonia, or atelectasis due to bronchial obstruction. In the absence of airway obstruction, the patient may be asymptomatic (1-7). Lung function may be impaired in patients with TBT. Maximal voluntary ventilation and peak expiratory flow rate were found to be most sensitive spirometric parameters for mild to moderate upper airway obstruction, while forced expiratory volume in first second (FEV_1) was found to be least sensitive. In these patients the shape of the flow-volume loop became abnormal earlier than spirometric measurements (*Figure 1*) (8-10). The presence of extrathoracic or intrathoracic fixed lesion results in flattening of both the inspiratory and expiratory parts of
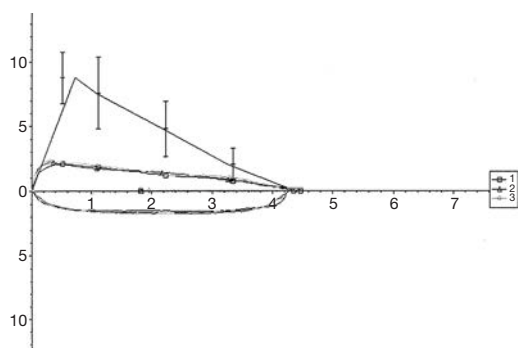
Figure 1 Flow-volume curve in the patient with tracheal tumor.

the flow-volume loop. An extrathoracic variable obstructing lesion results in the limitation of inspiratory flow expressed as a flattening in the inspiratory part of the flow-volume loop. Variable intrathoracic obstructing lesion results in a normal-appearing inspiratory limb of the flow-volume loop but the expiratory limb is flattened.

The body plethysmography and impulse oscillometry are useful in detecting increased respiratory resistance in patients with tracheal and bronchial tumors (11).

Delays in diagnosis of tracheal or endobronchial tumors commonly occur because the signs and symptoms caused by these tumors are nonspecific and chest radiographs are often considered unremarkable. The chest radiographic may demonstrate normal findings, a solitary pulmonary nodule, or bronchial obstruction with distal atelectasis or consolidation. Therefore, if there is clinical or radiographic suspicion of a TBT, further evaluation with computed tomography (CT) is recommended (5,12,13). CT imaging is the standard imaging tool for diagnosis and evaluation of tumor extent. It may demonstrate a tracheal or bronchial mass and/or associated findings of distal bronchial dilatation with mucoid impaction, post-obstructive pneumonia, subsegmental atelectasis or air trapping, indicating the endobronchial location of the tumors. More important, CT findings can exclude contiguous mediastinal and parenchymal lung involvement (12,13).

The diagnosis of TBTs has been significantly improved by recent advances such as the routine use of multi-detector CT (MDCT) with thin section reconstructions and techniques such as 2D minimum-intensity-projection and post-processing techniques like multi-planar reformation (MPR), volume rendering (VR) and virtual bronchoscopy (VB). The combination of these techniques could help to reveal tumor locations and morphologies, extramural invasions of tumors, longitudinal involvements of tumors,

morphologies and extents of luminal stenosis, distances between main bronchus tumors and tracheal carina, and internal features of tumors (*Figure 2*) (14,15). VB can show a real-like anatomical view of the tracheobronchial tree. Its images are in a similar fashion to conventional optical bronchoscopy. But, VB has some disadvantages, because it lacks the detail of real bronchoscopy and cannot show mucosal or submucosal extensions. However, VB is superior in bypassing any obstruction and therefore providing an excellent view distal to the high grade stenosis. This imaging modality provides information that may be beneficial in the management of patients with TBT (15-18). Magnetic resonance imaging (MRI) may have a role in individual patients, either when CT is unavailable or when radiation must be avoided in patients who need repeated imaging. It has been reported to be useful in adenoid cystic carcinoma (ACC) and fat containing lesions, as a lipoma and hamartoma (12). Endoluminal ultrasound may be used for evaluating the extent of airway tumor and its relation to the adjacent structure. It is possible to distinguish compression from infiltration of the airway by an extrinsic tumor, but detection of submucosal infiltration in the presence of a normal mucosal surface has so far not been described (19,20).

Another diagnostic tool that is increasingly being used in the diagnosis of various tumors that are suspected of being malignant is fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET). Increased FDG PET/CT uptake at the obstruction site is very suggestive of malignancy, while benign lesions show low FDG uptake (*Figure 3*) (21,22). Bronchoscopy is the main diagnostic tool for TBT because it allows direct visualization of tumor, tissue sampling and disease staging. Also, bronchoscopy reveals the localization, extent of TBT, as its relation to the surrounding structure (23).

The pulmonologist, thoracic surgeon and anesthesiologist should make multidisciplinary team and make the decision for TBT treatment. Good treatment results should be obtained using carefully planned and well-executed therapeutic approach. Therapeutic bronchoscopy with different interventional procedures (tumor resection, electrocautery, cryotherapy, argon plasma coagulation, laser, i.e.,) should open the blocked airways. Surgical treatment (sleeve resection, lobectomy, pneumonectomy) should be performed to obtain negative surgical margins while sparing lung parenchyma (7). The prognosis of TBTs is variable and depends on multiple factors, as location, malignant potential, co-morbidities, lymph node involvement and invasion of mediastinal vital organs.

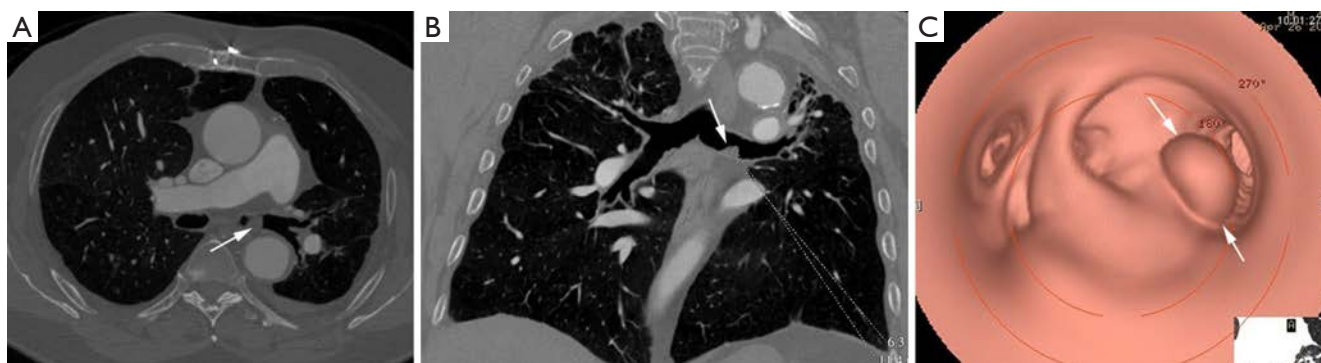TBTs are rare in children, more often malignant than

Figure 2 Axial (A) and coronal MPR (B) images shows tumor mass in left main bronchus (arrows). Virtual bronchoscopy (C) of the same patient shows a tan spherical, smooth-surfaced tumor in left main bronchus (arrows).

Figure 3 Squamous cell carcinoma of trachea. Axial (A) and coronal MPR (B) images show eccentric soft tissue mass with regular margins involving trachea with mediastinal extension (arrow in A,B). PET CT shows high FDG uptake (arrow) suggesting malignancy (C).

Table 1 Classification of tracheobronchial tumors

Origin of tumor	Primary malignant tumors	Benign tumors
Surface epithelium	Squamous cell carcinoma (SCC), adenocarcinoma, neuroendocrine tumors (carcinoid tumor, large cell neuroendocrine tumors, small cell carcinoma)	Squamous cell papilloma, papillomatosis
Salivary glands	Adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma (MEC), epithelial-myoepithelial carcinoma (EMEC)	Pleomorphic adenoma, mucous gland adenoma, oncocytoma
Mesenchyme	Sarcoma, malignant lymphoma	Hamartoma, leiomyoma, lipoma, fibroma, neurogenic tumors
Direct invasion (most common): thyroid cancer, laryngeal cancer, lung cancer, esophageal cancer		
Hematogenous metastasis: breast cancer, renal cell carcinoma, colon cancer, melanoma		

benign, with wide array of pathologic findings. In childhood, TBT presents with respiratory symptoms not improving with antibiotics and bronchodilators. Some patients have symptoms of recurrent pneumonia. Carcinoid tumors usually manifest as cough and recurrent wheezing. The wheezing is thought to be attributable in part to the obstruction but also to serotonin release by the tumor in the respiratory tract (24,25).

Characteristics of specific TBTs

Tumors in the tracheobronchial tree can be classified as primary malignant tumors, secondary malignant tumors, or benign tumors. Primary malignant tumors commonly originate from surface epithelium or the salivary glands, while benign tumors from mesenchymal tissue (*Table 1*) (6).
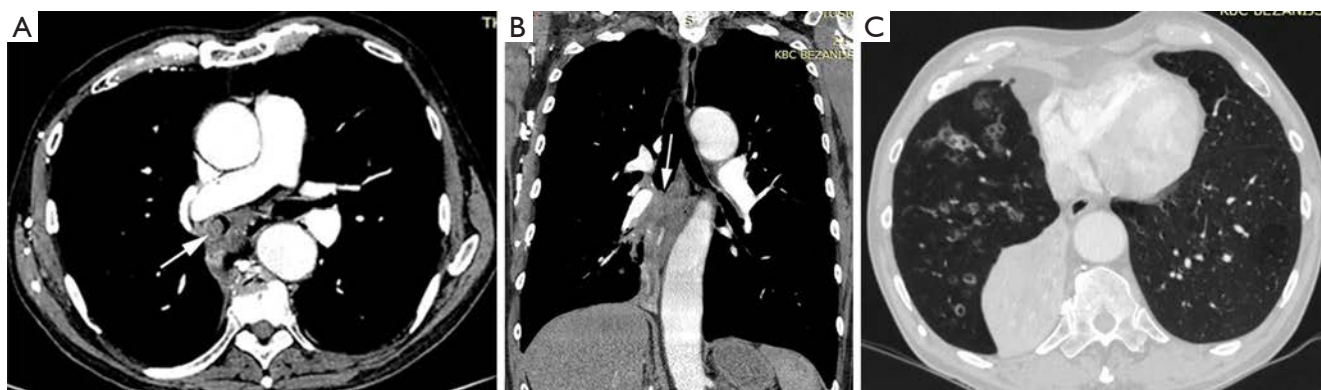
Figure 4 Squamous cell lung carcinoma. Contrast enhanced axial (A) and coronal MPR (B) images show obstructing tumor mas in right lower lobe (arrow in A,B) with distal atelectasis(C).

Malignant tumors

Most tumors of the tracheobronchial tree are malignant, whereas benign tumors are very rare. The predominant types of malignant TBT are squamous cell carcinoma (SCC), small cell carcinoma, carcinoid tumor and mucoepidermoid carcinoma (MEC). SCC and small cell carcinoma are most common types of primary lung carcinoma which originate from the large bronchi. Both tumors are highly associated with cigarette smoking. Symptoms are related to the degree of bronchial obstruction an include cough, hemoptysis. Secondary malignant tumors in the airways are uncommon and may occur as a result of hematogenous spread or direct invasion by a malignancy of an adjacent organ. Airway invasion by primary neoplasms arising from adjacent organs is more frequent than hematogenous metastases. Local tracheal invasion from adjacent cancers of the esophagus, thyroid, or lung is more common than hematogenous spread to the mucosa (4,21).

Primary malignant tumors
SCC

Primary tracheal neoplasm is very rare. Reported frequencies range from 0.075% in autopsy series to 0.19% of all patients with malignancies of the respiratory tract. Ninety percent of all adult primary tracheal neoplasms are malignant with common histopathological patterns comprising of SCC, ACC, carcinoid, MEC, and papilloma (13). SCC are aggressive neoplasms associated with smoking, with a peak incidence between the ages of 50 and 70 years (12,14). SCC is the most common tracheal tumor and is two to four times more common in men. It is histologically identical to lung SCC. SCC is commonly asymptomatic. Symptoms usually

appear when the tumor occludes more than 50% of the airway diameter and include cough, hoarseness, dyspnea, hemoptysis, and wheeze (6,26-28). At CT, the tumor may appear as a polypoid lesion, a focal sessile lesion, eccentric narrowing of the airway lumen or circumferential wall thickening generally in the lower third of trachea. This tumor typically has irregular margins as it arises from the surface epithelium. It may invade mediastinum by direct extension or lymphatic spread (12,13,15).The majority of SCCs of the tracheobronchial tree show high uptake at FDG PET (*Figure 3C*) (21).

Endobronchial SCC causes airway obstruction by mass itself and leads to pulmonary atelectasis or lobar collapse. SCC is the most common cell type which cavitate, in approximately 10% of cases (16). At CT, endoluminal mass has the same appearance as in trachea (*Figure 4*). The primary mass may be differentiated from atelectatic lung and mucus regarding the different contrast enhancement or by different signal intensity on MRI. Small cell cancer is the second most common lung cancer arising in the central bronchi. Bronchial obstruction is much less common with small cell carcinoma than with SCC. The most common imaging finding in small cell carcinoma is extensive hilar or mediastinal lymphadenopathy secondary to early metastasis (13,16).

Carcinoid tumors

Bronchial carcinoid tumors account for over 25% of all carcinoid tumors and for 1–2% of all pulmonary neoplasms. Typical pulmonary carcinoid tumors are more frequent with approximately 80–90% of cases (12). It usually involves the main, lobar, or segmental bronchi. Bronchial carcinoids range from low-grade typical carcinoids to intermediate-grade atypical carcinoids to high-grade small cell carcinomas and demonstrate a wide spectrum of clinical
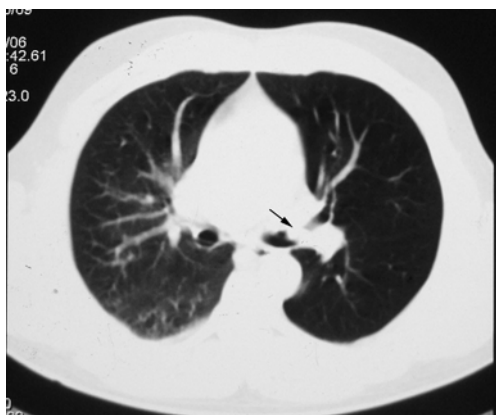
Figure 5 Chest CT of patient with carcinoid tumor. CT scan shows an oval tumor inside the left upper lobe bronchus arrows) and hyperlucency of the same lobe.

manifestations and histologic features. Bronchial carcinoids affect male and female patients equally with a mean patient age of 45 years (2,29-31). Patients with atypical carcinoid are significantly older than those with typical carcinoid while patients with bronchial carcinoids are younger than those with bronchogenic carcinoma (32). Large series showed that smoking is associated with atypical but not with typical carcinoids (31). Most series reported about 25% of patients without symptoms, so that bronchial carcinoids are an incidental finding (32). Most of symptoms and signs are the consequence of bronchial obstruction and include dyspnea, cough, recurrent pulmonary infection, fever, expectoration, wheezing, hemoptysis, and chest pain. Some patients are misdiagnosed as asthma. In series of Filosso *et al.* a total of 14.2% of patients had been treated for asthma for up to 3 years before the tumor was discovered (31). Hemoptysis occurs in at least 50% of patients, reflecting the rich vascularization of these neoplasms. Paraneoplastic syndromes are rare and include carcinoid syndrome, Cushing's syndrome, and ectopic growth hormone-releasing hormone secretion (12,30,31). Because of the central location of carcinoids, initial chest-ray may demonstrate normal finding or findings related to bronchial obstruction like atelectasis, obstructive pneumonitis or air trapping (*Figure 5*). Central bronchial carcinoids most common are manifested as a hilar or perihilar mass (2,29,32,33). The mass is usually a sharply bordered, round or ovoid lesion and may be slightly lobulated at radiography and CT. On CT, endobronchial carcinoid tumor appears as a well-defined spherical or oval mass with a slightly lobulated border and frequently intensely enhanced (*Figure 6*).

However, not all carcinoids show contrast enhancement but enhancement alone does not allow differentiation of bronchial carcinoid from bronchogenic carcinoma (33-35). Extraluminal component of the tumor which is not visible bronchoscopically, could be presented at CT. Furthermore, typical carcinoids are smaller than atypical carcinoids which may have irregular contours and less uniform contrast enhancement (36). Peripheral carcinoids can manifested as nodules, non-segmental infiltrates or pleural effusion. In reported series nodules were most common manifestation of peripheral carcinoid tumors (2,34). The eccentric calcifications, especially in central carcinoids, are usually not identified at conventional radiography but are clearly visible at CT in up to 26% (12). It has been reported that an ultrafast contrast-enhanced magnetic resonance (MR) imaging shows a pronounced and rapid increase in signal intensity in bronchial carcinoids (12,13). Both typical and atypical carcinoids may be associated with hilar or mediastinal lymphadenopathy due to hyperplasia from recurrent pneumonia or metastasis (2,37). Most studies have been reported that carcinoid tumors may show increased FDG uptake due to high metabolic activity and malignant potential but still lower than would be expected for malignant tumors (21,22). Scintigraphy with ^{111}In-octreotide has shown valid uptake in primary tumors and the ability to detect early recurrences and metastases even in asymptomatic patients which might be a useful tool for the staging in the future (31). Since most bronchial carcinoids are in a central location they are within reach of a bronchoscope. These tumors have a characteristic bronchoscopic appearance as smooth, cherry red, polypoid endobronchial nodules (2).

Salivary glands malignant tumors
Primary salivary gland-type tumors of the lung are rare, accounting for fewer than 2% of all lung cancers. These tumors characteristically grow intraluminally in the central airway, tend to occur in non-smokers and younger patients and have a much better prognosis than the more common types of lung cancer (adenocarcinoma and SCC). The most common histologic type is ACC, comprising about two thirds of the cases, whereas MEC comprises about a third and only a few EMEC primary salivary gland-type tumors of the lung have been described in the literature (20,38,39).
ACC
ACC is the most common salivary-type tumor of large airways and the second common primary tracheal tumor with a prevalence of 0.04–0.2% (19). It should be

Figure 6 Typical carcinoid tumor. Contrast-enhanced axial (A), MPR (B) images and coronal reconstructed MinIP (C) show a well-defined, soft tissue nodule (arrow) in the left main bronchus.

considered as differential diagnosis, especially in younger adults with tumors in trachea and/or large bronchi (40-42). Most studies reported female predominance and no association with smoking (43). Since the longitudinal extent is typically greater than the cross-sectional area it may even involve the entire trachea and extend into the main bronchi. It also arises in main stem or lobar bronchi without tracheal involvement (13,44). Symptoms in patients with ACC are non-specific and some studies divided them in two groups: those related to airway obstruction and symptoms associated with lung infections. Dyspnea, cough, stridor, wheezing, and hemoptysis are the most common complaints. Unfortunately, these signs and symptoms often lead to a misdiagnosis as asthma or chronic bronchitis which delays in reaching a definitive diagnosis. Therefore, most patients present with locally advanced disease. But, despite this fact, prognoses are good unless metastases are detected (45).

The CT scan is a useful imaging procedure for ACC. It is highly accurate in the assessment of the tumor location, extra luminal extensions, carinal involvement and distant metastasis. At CT, ACC appears as a focal mass in the trachea or main bronchi with a smooth border as it arises from submucosa. It may involve more than half of the airway circumference. This tumor can also be differentiated from MEC because of its frequent extra-luminal extension. Lymphadenopathy and distant metastases are uncommon and the local recurrence is most common (13).

The largest imaging studies reported that FDG uptake in primary salivary gland-type tumors of the lung is variable, depending on the grade of differentiation; like in other indolent tumors (39,43). Timely diagnosis of ACC is important because prognosis is improved with early treatment (21,22).

MEC

MEC of tracheobronchial tree is rare-occurring tumor, comprising only 0.1–0.2% of all lung malignancies and affecting equally males and females at median age of 40 years (from 3 to 78 years), not correlated with smoking. It arises from minor salivary glands lining the tracheobronchial tree and originates more common in the lobar bronchi than in the trachea or main bronchi. Fewer than 15% of cases occur in the lower trachea and rarely tumor presents as an isolated peripheral pulmonary nodule. On the basis of histologic criteria, this tumor is classified as either low grade or high grade (46,47). Several studies (43,47) reported that patients with low grade MEC are younger than those with high grade tumor. Symptoms of MEC are nonspecific and depend on the degree of bronchial obstruction. Cough, hemoptysis, pneumonia and fever were reported as most common clinical symptoms of MEC, although one third of patients can be asymptomatic (47). Radiographic features of MEC are related to bronchial obstruction. In some cases, solitary peripheral nodule can be seen. CT enable visualization of endoluminal tumor mass, even when the tumor is located within a segmental bronchus. It appears as a non-spherical, smooth, lobulated, mild enhanced intraluminal mass adapting to the branching features of the lobar bronchus. It is often associated with dilated distal bronchi, mucoid impaction and distal atelectasis. Peripheral nodules appear as a smooth round nodule less than 2 cm in size. Punctate calcifications within the tumor are seen in half of the patients. Metastases to the regional lymph node are rare, and the prognosis is excellent (13,39,48). Reported series showed variable amounts and patterns of FDG uptake
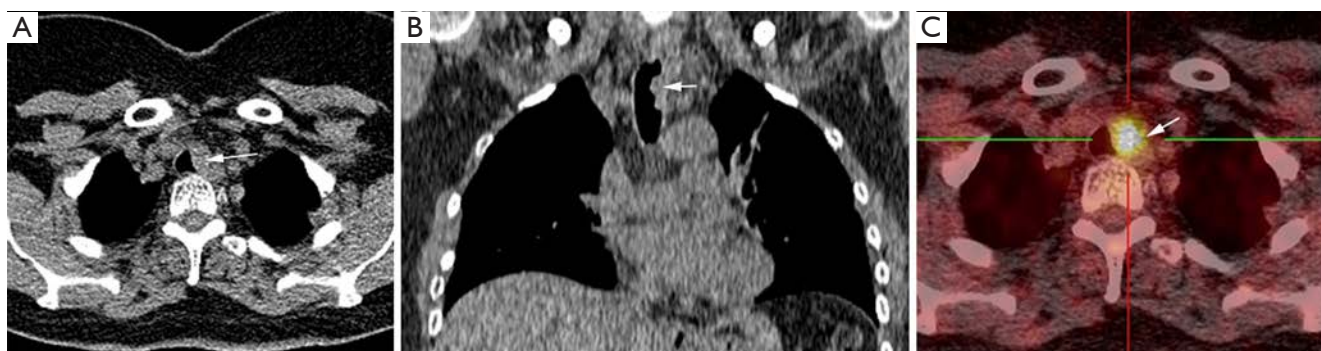
Figure 7 Tracheal metastasis from colorectal cancer. Axial (A) and coronal MPR (B) images show soft tissue mass causing reduction of tracheal lumen (arrows in A,B). PET CT (C) image shows increased FDG uptake in lesion (arrow).

in MEC resembling bronchial carcinoid. In doubtful cases additional ^{68}Ga-DOTATOC PET CT could be performed. Positive finding suggest typical carcinoid, and negative MEC. MECs in the central airways with high FDG uptake may be difficult to distinguish from bronchogenic carcinoma (12,21,49).

At bronchoscopy, MECs of the trachea or bronchi usually appear as exophytic intraluminal, pink, highly vascularized mass which can be sessile polypoid with a broad base connected to the bronchial wall or pedunculated with a well-formed stalk. This finding may resemble carcinoid tumor (50).

Metastases

Metastatic involvement of the trachea and large airways is rare and may occur as a result of hematogenous spread or direct invasion by a malignancy of the lung, larynx, esophagus, thyroid gland, or mediastinum. The most common primary tumors that spread hematogenously to the large airways are breast, colon, kidney, lung and melanoma (51). At CT, these tumors can present as solitary or multiple polypoid nodules (*Figure 7*) with or without the "glove-finger" appearance, or as eccentric wall thickening (21). In rare cases when the metastasis is solitary, it is indistinguishable from a primary airway tumor (i.e., SCC, ACC, or carcinoid).

In cases of direct airway spread from a primary tumor, the important clue to the diagnosis is to establish that the tumor is centered outside the airway, for example, in the esophagus, lung, or thyroid. A history of primary adenocarcinoma or melanoma suggests metastatic involvement of the airways. In most cases, the extramural source of an airway tumor is apparent at CT (13,52).

The degree of FDG uptake depends mostly on the

metabolic activity and degree of differentiation of the primary tumor. Since the majority of malignancies have high metabolic activity, FDG PET usually shows intense uptake (12,21).

Benign endobronchial tumors

Benign tumors of the tracheobronchial tree are quite rare and constitute 2% of all lung tumors. Histologically, the most frequent benign TBTs are hamartomas and papillomas. Less frequent benign neoplasms are leiomyomas, lipomas, chondromas, and neurogenic tumors. These tumors are slow growing and usual presentation is related to bronchial obstruction. Benign lesions of the trachea often remain undiagnosed for months or even years, misdiagnosed as COPD or asthma (2,3,5,53).

The clinical and radiographic features of benign TBT cannot be often differentiated from those of malignant tumors. Many of these lesions have similar radiographic manifestations which are often non-specific and include atelectasis, pneumonia, bronchiectasis, and mediastinal shifts. Early recognition and diagnosis of these tumors may allow conservative treatment and excellent patient outcome (3,5).

Hamartomas

They are the most common type of benign endobronchial neoplasms (70% cases) with an incidence in general population between 0.025% and 0.32% (3). This tumor is most commonly located intrapulmonary and endobronchial location is very rare with an incidence of 1.4% in the largest review series (23,54). Tracheal hamartoma is extremely rare with less than 20 cases of adult found in literature (12,55). Tracheobronchial hamartoma are believed to be
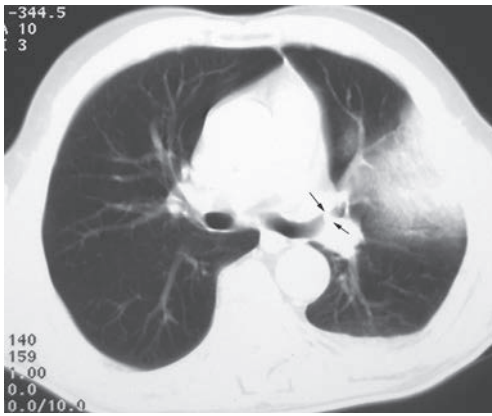
Figure 8 Endobronchial hamartoma presented as endobronchial mass in lingular bronchus (arrow) and distal pneumonia on axial CT scan.

developmental in origin but more recent evidence points to a true neoplastic origin. Large series reported that hamartomas occur more frequently in older males with the peak in the sixth decade suggesting that inflammatory lung disease and smoking influence the incidence of hamartoma (3). These tumors are composed of a mixture of different tissues like cartilage, bone, fat and smooth muscle. Cartilaginous elements predominate and content of fat is higher in endobronchial than intraparenchymal lung hamartoma (13,23). Unlike pulmonary hamartomas, endobronchial hamartomas are often symptomatic. They usually manifested with symptoms of bronchial obstruction like cough, recurrent infection, wheezing, hemoptysis and dyspnea (2,53,56). Chest radiographic is non-specific and the two most common manifestations are consolidation and atelectasis caused by proximal airway obstruction. Endobronchial hamartoma appears on CT as a focal heterodense mass because of its various tissue components. CT findings such as internal fat and "popcorn" calcification together are typical of endobronchial hamartoma. However, nodules without these findings may be difficult for distinguishing from malignancies with CT alone. Postobstructive pneumonia or atelectasis can be present (*Figure 8*) (13,40,57). Hamartoma typically shows little or no radiotracer uptake on FDG PET. However, atypical pulmonary hamartoma may have increased FDG accumulation, thereby mimicking a malignancy. This false-positive finding could be explained by increased metabolic activity of the tumor (21). Bronchoscopic examination shows a polypoid or pedunculated sharply marginated mass with a smooth and yellowish surface without submucosal

involvement (23,53).

Chondromas

Endobronchial chondromas are extremely rare benign tumor, which arises from the bronchial cartilage. As they have been historically misclassified as hamartomas, the true incidence of chondromas is still unknown. Endobronchial chondromas may be part of the Carney triad. Isolated endobronchial chondromas are less frequent than in Carney triade and can occur anywhere in the tracheobronchial tree with a higher prevalence in trachea (58). In Carney triad, chondroma affects young females whereas isolated chondromas affect males between third and fifth decade (53,58). Clinical manifestations of endobronchial chondroma depend on the extent of mechanical obstruction of bronchus. Symptoms are nonspecific, such as cough, sputum, fever, or dyspnea on exertion. Radiologic image is usually non-specific and the differential diagnosis includes hamartomas, tracheal amyloidosis, lung cancer and mucus plugs. The presence of bone and fat tissue on a chest CT suggests hamartoma. Well differentiated chondrosarcoma can be sometimes misdiagnosed as chondroma. The presence of tissue invasion, metastatic lesions are suggestive of chondrosarcoma or other metastasis (58-60).

Lipoma

Bronchial lipoma is extremely rare benign tumor with an incidence from 0.1% to 0.5% of all lung tumors and 1.4–13.0% of benign tumors of the lung (61). In a recent review of the English and Japanese literature on endobronchial lipomas, Fujino *et al.* reported 95 cases. An endobronchial location is twice as common as its parenchymal counterpart, and is often found in the left main-stem bronchus. Endobronchial lipomas consist of mature adipose tissue, some fibrous components lined with normal bronchial epithelium, sometimes developing squamous metaplasia (3,53,62). Largest series reported that endobronchial lipomas occur more frequently between the fifth and sixth decade of life onward, being more prevalent among males and obese persons (62). It has been reported that smoking and obesity are significant risk factors for endobronchial lipoma. The clinical symptoms of endobronchial lipoma are caused by airway obstruction and patients present with cough, hemoptysis, recurrent pneumonia, wheeze, or dyspnea. The duration of symptoms before diagnosis ranged from one month to few years (2,63). Radiographic finding is non-specific. In large series, most common chest X-ray and CT finding was atelectasis followed by consolidation
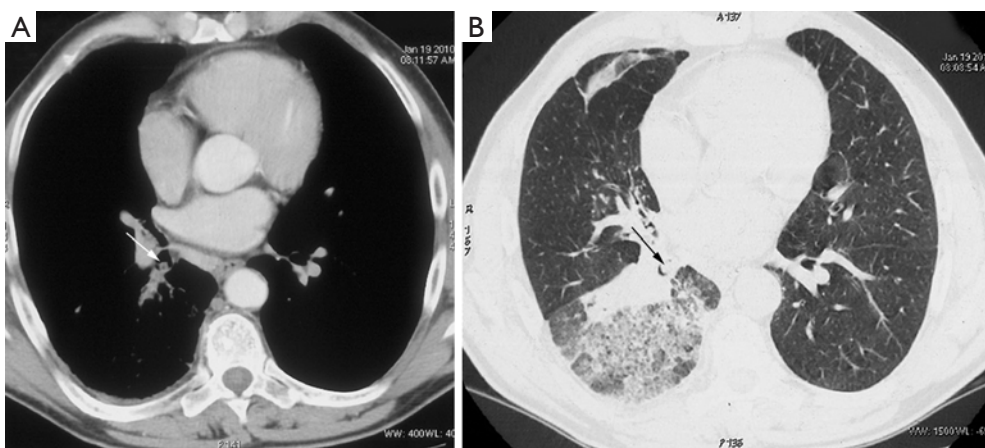
Figure 9 Endobronchial lipoma. Axial CT scans in soft tissue (A) and lung window setting (B) shows round tumor in posterior segmental bronchus of the right lower lobe and signs of inflammation.

(*Figure 9*). Other less frequent findings were tumor shadow, air trapping and pleural effusion. The size of the lesions reported in the literature varies from less than 1 cm to more than 7 cm (2,62,63). The CT findings of a homogeneous mass with fatty density and no tumor contrast enhancement are considered diagnostic (40,64). Magnetic resonance imaging enables accurate determination of the morphological characteristics of the mass with a hypersignal on the T1-weighted images and an intermediate signal on the T2-weighted images, compatible with normal fat. Endoscopically, the tumor appears as a soft gray, yellowish, mostly pedunculated mass that sometimes resists biopsy because of a firm capsule (12,23,53).

Mucous gland adenoma

Mucous gland adenoma is one of the rarest epithelial neoplasms which comprises of less than 0.5% of all lung tumors with same essential histological features and prognosis like salivary glands tumors of the neck (20,40). MGAs arise from mucosal seromucous glands and ducts of trachea or bronchi (38,53,65). It occurs commonly in lobar or segmental bronchi without predilection to the right or left lung. MGAs are not associated with smoking and occur in children as well as in adults. Largest series of ten patients reported mean age of 52 years (65). If there is no obstruction, the patient is asymptomatic. Enlargement of tumor leads to obstructive symptoms with the clinical picture of chronic bronchial obstruction. More commonly, the patient seeks treatment because of cough and hemoptysis, chest pain, dyspnea on exertion, localized wheezing, recurrent pneumonia, or atelectasis

(66,67). The radiologic findings may include a normal chest radiograph, a solitary pulmonary nodule, or bronchial obstruction with distal atelectasis or consolidation. The CT findings of bronchial MGA show well-defined intraluminal mass, typically with an air meniscus sign, suggesting an intraluminal location (66). Bronchoscopic examination usually reveals pedunculated or sessiled, smooth-surfaced polyp in the lumen of larger bronchi (65).

Papilloma

Bronchial papillomas (BP) are rare TBT that account for 0.38% of all lung tumors and 7% to 8% of all benign lung tumors. Papillomas are normally classified into three separate categories: multiple papillomas, inflammatory polyps, and solitary papillomas. In adults, solitary BP are more common, prevalent in smokers, middle aged men (5,53). Multiple BP of the upper airways, often referred to juvenile laryngotracheal papillomatosis reflects neoplastic growth secondary to infection with human papillomavirus types 6 and 11 (68). They are more common in the pediatric population. Solitary BP of the bronchus is classified according to histologic features into three groups: squamous cell papilloma, glandular papillomas, and mixed (squamous cell and glandular) papillomas (68). They appear as a discrete polyploid nodule within the trachea, the lobar, or the segmental bronchi. The BP arises from the mucosal surface, and measure between 0.7 and 2.5 cm in diameter. They often cause narrowing of airway lumen which may lead to atelectasis, air trapping, post-obstructive infections, and bronchiectasis. The clinical history may last from a few months to two years of
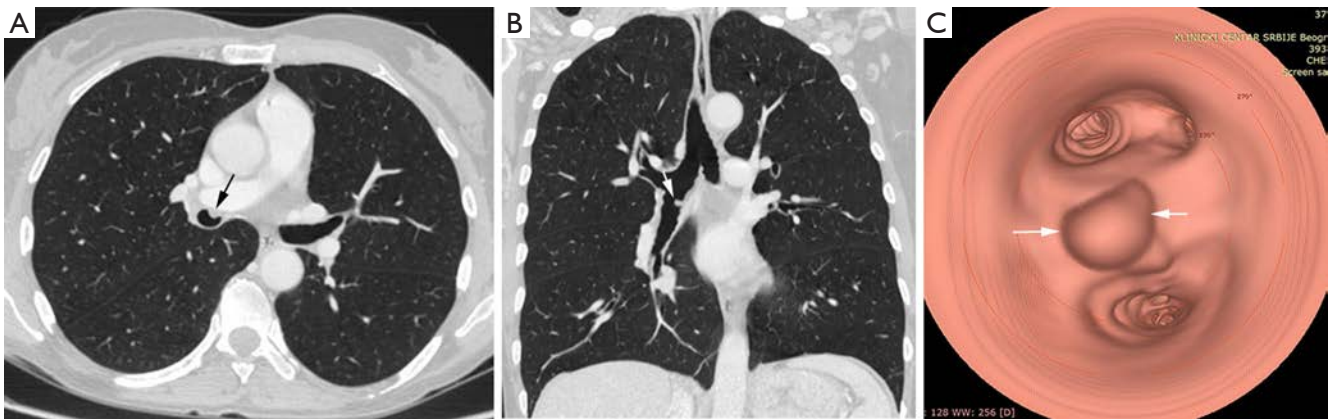
Figure 10 Bronchial papilloma. Axial (A), coronal MPR image (B) show a smooth polypoidal soft tissue mass arising from the anterior wall of right lower bronchus (arrow). Virtual bronchoscopy (C) shows the intraluminal mass lesion with smooth surface (arrow).

intermittent attacks of cough hemopthysis and dyspnea or history of repeated or unresolved pneumonia (68,69). The radiological manifestations depend on the size and location of the papilloma. Many of BP in trachea or main bronchi are not detected on the chest radiograph but CT may provide useful information. CT findings usually consist of a polypoid mass in the airway lumen and distal atelectasis and obstructive pneumonitis in the case of complete obstruction (*Figure 10*). Partial bronchial obstruction may result in reflex vasoconstriction leading to decreased perfusion and hyperlucency of the affected lung or lobe. Involvement of the distal airways and parenchyma can present with multiple, frequently cavitate nodules, measured up to several centimeters in diameter. Smoking, age above 40 years, and infections with human papillomavirus serotype 16 or 18 are risk factors for malignant transformation of benign squamous BP (70-72).

Primary endobronchial leiomyomas

Primary endobronchial leiomyomas (EL) are among the rarest of benign tumors of the respiratory tract accounting for approximately 0.66% of all benign lung neoplasms. These neoplasms can occur in lung parenchyma, trachea or bronchi. Endo-bronchial lesions constitute approximately 33% of all pulmonary leyomiomas (73). They are thought to derive from the smooth muscles of the bronchial tree. Origin from the areas of cicatricial fibrosis has also been proposed. Bronchial leiomyomas are benign tumors which predominantly occur in the third and fourth decade of life without gender predilection, although slight female preponderance has been reported in pulmonary leyomiomas (53,74). Patients with this condition have respiratory

symptoms due to partial or complete airway obstruction which may stimulate asthma or be complicated with bronchiectasis and recurrent lung infection. Most common symptoms are cough, hemoptysis, dyspnea and malaise. Intermittent or constant dyspnea and wheezing are the most common symptoms of tracheal leiomyoma. The chest radiography may be normal in patients with small endobronchial tumor or shows solitary round mass or pneumonic infiltration, mediastinal shift, and collapse of lung to unilateral emphysema or hyperlucency according to the bronchial obstruction due to the tumor. On CT scans, tumor most commonly manifested as a homogeneously enhancing endo-luminal tumor with intraluminal growth. Sometimes, an iceberg appearance of the tumor (small intraluminal component and large extra-luminal component) can be found. Endobronchial nodule is often associated with post-obstructive pneumonia or atelectasis (53,73). Bronchosopy is greatly helpful in locating the exact site of the tumor and to obtain histopathological diagnosis. Tumors within the tracheobronchial tree appear as fleshy polypoid masses that protrude intraluminally and are attached to a wide base. A pre-operative histological diagnosis would certainly help in planning the site and resection of the tumor rather than radical resection of the lung.

Other endobronchial tumors

Other TBT are very rare and usually described as case reports or institutional experience. They include various tumors. Some of them originate from surface epithelium (large cell neuroendocrinal tumors), some originates from

salivary glands (oncocytoma, myoepithelial carcinoma, pleomorphic adenoma, etc.) and some originates from mesenchyma (schwannoma, fibrosarcoma, chondrosarcoma, T-cell lymphoma). They are usually diagnosed incidentally on bronchoscopy or CT. They tend to have similar clinical presentation as cough, dispend, hemoptysis or signs of tracheobronchial obstruction (19).

Conclusions

A wide spectrum of tumors can occur in the tracheobronchial tree, including primary malignant tumors, secondary malignant tumors, and benign tumors. Except SCC and small cell lung cancer, tumors and tumorlike conditions of the central large airways are uncommon. Careful clinical evaluation, imaging and endoscopic examination are essential for the confirmation of endoluminal tracheobronchial lesions. Recent technical advances in immunohistochemistry and MDCT techniques (2D minimum-intensity-projection and 3D volume images) can very accurately define the location as well as intra- and extra-luminal extent of tracheal and endobronchial tumors. These techniques have become valuable tools for the clinician to assist with the diagnosis and planning of therapy for TBT.

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Footnote

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Review of tracheobronchial foreign body aspiration in the South African paediatric age group

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Abstract: Children, and in particular young children under the age of three, are the most vulnerable for aspiration and ingestion of foreign bodies (FBs). The Red Cross War Memorial Children's Hospital in Cape Town is the only children's hospital in South Africa and is unique in having a dedicated trauma unit for children under the age of 13 as part of its institution. Core activities of Childsafe South Africa (CSA), located at the hospital, are data accumulation and interpretation, development of educational programmes, health inculcation and advising in legislation involving child health. To achieve this task, CSA works in close co-operation with government, industry, non-governmental and community predicated organisations, community groups and individuals. A database of all children treated for trauma at CSA has been maintained since 1991; it currently contains detailed information of over 170,000 injuries in children under the age of 13. This review consists of a literature review combined with data from our database and aims to provide information on our experiences with tracheobronchial aspiration of FBs in children.

Keywords: Aspiration; bronchus; children; trachea; South Africa; review

Introduction

Children, and in particular the very young, are the most vulnerable for aspiration and ingestion of foreign bodies (FBs) (1).

Although the spectrum of FBs varies from country to country, depending on the diet and customs of the population, the most common foreign body aspiration (FBA) causing injuries are from diminutive food items (2). Case reports, cases series and data emanating from death certificates testify that nuts and seeds could represent an earnest threat being not only the most documented FB, but also frequently involved in cases presenting with complications and requiring hospitalization (3).

Aspiration of a FB into the air passages conventionally occurs in older infants and toddlers. Boys are affected more than girls in a ratio of 2:1 (4).

FBA is a prevalent cause of pathology in children, particular in those younger under 3 years of age. It has been estimated that in the year 2000, FBs, either ingested and/or aspirated were responsible for over 17,000 visits to health facilities of children under the age of 15 in North America (5).

While the mortality has been typically high in previous centuries, (almost a quarter of all cases), with the advance of modern bronchoscopy techniques, current mortality has significantly declined over the last 25 years (6).

It has been estimated that the vast majority of FB aspiration takes place in children under the age of 4, while the peak incidence seems to occur between the age of 12 and 24 months (7-14). These children can move around

Table 1 Location of FBA in children

Location	Percentage (percentages rounded off)
Larynx	3
Trachea and carina	13
Right lung (total)	60
Main bronchus	52
Lower lobe bronchus	6
Middle lobe bronchus	<1
Left lung (total)	23
Main bronchus	18
Lower lobe bronchus	5
Bilateral	2

and are able and prone to explore the outside world with their mouth, putting any object they can get hold of within their mouth, while they still lack proper molars to grind objects to smaller (and less dangerous) pieces.

Other predisposing factors for FBA at this young age include access to unsuitable foods or tiny objects, all kinds of other active behaviour while eating. Above all, children are far more vulnerable to aspiration of a FB due to the small diameter of their airway, prone to easily be obstructed (15). In adolescents and adults, neurodevelopmental delays (16), low level of consciousness, and drugs and alcohol will increase the risk of FBA (17).

In paediatrics, commonly aspirated FBs are nuts, victual particles, equipment, and parts or bits of toys, peanuts (36–55% of FBs aspirations in civilized countries), seeds and popcorn (9-11,13,14).

Aliment parts are the most widely recognized objects aspirated by newborns and babies, while non-food particles as pins and coins are mostly present in elder kids (2,18-20). Inflatables toys or other objects (e.g., inflated gloves or condoms) are the most prevalent objects in lethal FBAs (15).

Factors that make FBs more perilous include roundness (round objects are most liable to cause consummate airway obstruction and asphyxiation), failure to break asunder facilely, compressibility, and smooth, slippery surface (15). The effects of tablet aspiration depend on the properties of the medication. Certain medications such as iron or potassium may dissolve in the airways and cause excruciating inflammation and eventually stenosis, so early diagnosis and timely extraction is consequential to minimize long-term consequences (21,22).

The majority of FBAs in children are located in the bronchi (7,11,23). Laryngeal and tracheal FBs are less common. In a large case series of FBA aspirations in children, the sites of the FB are shown in *Table 1* (7).

Although most aspirated FBs are located in the bronchi, sizably voluminous, bulky FBs (e.g., aliment), or those with sharp, aberrant edges may also become lodged in the larynx (11,24). This is particularly prevalent in infants younger than one year. Tracheal narrowing or impotent respiratory effort may predispose to tracheal FB (11). Compared with bronchial FBs, laryngo-tracheal FBs are associated with incremented morbidity and mortality (24,25).

Clinical presentation

Youngsters frequently move and giggle while they are eating and don't focus on masticating or gulping. In addition, the neurological-motor mechanism controlling swallowing may also be still underdeveloped, disqualifying it to give appropriate control to eschew nourishments or different materials to enter air passages.

Roughly 75% of upper airways FBs in the children happen in kids less than 3 years. Most FBs are sufficiently small to pass to the trachea.

Because of the wide calibre of the trachea contrasted with the cricoid cartilage, only few FBs lodge within the trachea. Consequently most FBs will pass through the trachea to lodge within the bronchi.

In children less than 5 years, non-food particles are less common than food particles, while in elder children non-food particles dominate.

A detailed history and a thorough clinical examination are very important in assessing children that potentially aspirated a FB (26).

It is not uncommon following aspiration of a FB that a "silent era" to occur. Only when time progresses, the FM may cause erosion and/or inflammation. This condition could be accompanied by fever, cough discomfort and haemoptysis. Serious lung infections may develop later (4,26).

The signs and symptoms of FBA vary according to the location of the FB (27,28) (*Table 2*).

Delayed diagnosis—patients who present days or weeks after the aspiration often develop symptoms due to complications cognate to the presence of the FB, such as infection and inflammation of the airway. Thus, they may present with fever and other signs and symptoms of pneumonia. In the absence of a history of choking, FBA may not be suspected. These patients with occult FBA

Table 2 The signs and symptoms of FBA vary according to the location of the FB

Location	Signs and symptoms
Laryngotracheal	Relatively rare (5–17% of FBs) but are categorically liable to be life-threatening. Symptoms include stridor, wheeze, and dyspnea, and sometimes hoarseness. FBs in this location are most liable to present with acute respiratory distress, which must be addressed promptly. Laryngeal FBs or sizably voluminous perforating FBs with sharp edges withal may cause symptoms cognate to the esophagus
Large bronchi	The customary symptoms are coughing and wheezing. Hemoptysis, dyspnea, choking, shortness of breath, respiratory distress, decremented breath sounds, fever, and cyanosis may withal occur (7,8,29)
	The right main bronchus is the most common location (45–55% of FBs), followed by left bronchus (about 30–40% of FBs), and bilateral bronchi (1–5%)
Lower airways	Children with these FBs may have little acute distress after the initial choking episode

FBA, foreign body aspiration.

Figure 1 Aspirated metal screw positioned within the right main bronchus and with the pointed tip in the trachea while the blunt end pointing downwards (the most common orientation) (4).

may amend with antibiotic therapy. However, the infiltrate on chest radiograph customarily does not resolve, and recurrence of pneumonia is common.

One reason for delay in diagnosis is that children with lower airway FBs may present with subtle or nonspecific symptoms (30). As a result, they may come to medical attention only when they develop dyspnoea, wheezing, chronic cough, or recurrent pneumonia (31).

Other factors contributing to diagnostic delay include unwitnessed aspiration, a decision by the parents or physician not to pursue evaluation once the acute choking episode has resolved, and misinterpretation of symptoms as evidence fortifying the diagnosis of *de novo* pneumonia, asthma or asthma exacerbation, or bronchiolitis (11,30,32).

Life-threatening FBA—if a child presents with consummate airway obstruction (i.e., is unable to verbalize or cough), dislodgement utilizing back blows and chest compressions in infants, and the Heimlich manoeuvre in older children, should be endeavoured. In contrast, these interventions should be eschewed in children who are able to talk or cough since they may convert a partial to a consummate obstruction (11). For the same reason "blind" sweeping of the mouth should be evaded.

The recommendations of the American Heart Sodality (AHA) regarding interventions for choking represent the standard in acute life-threatening events (33).

Diagnosis

Posteroanterior and lateral chest radiographs (*Figure 1*) are acquired to assess a youngster suspected of FB aspiration. Posteroanterior and lateral neck radiographs are subsidiary for distinguishing tracheal radiopaque particles. Chest radiographs on respiration can be of use. Expiratory radiographs can demonstrate air which caught underneath the obstacle, bringing about emphysema of the included part; contralateral shift of the mediastinum can also be seen.

Radiographs may demonstrate any other inflammatory lung problems. In any case, endoscopy remains the gold standard for both discovery of FBs and treatment by extraction (4,26). Flexible rather than rigid bronchoscopy may be utilized for diagnostic purposes in cases in which the diagnosis is obscure, or if the FBA is known but the location

Table 3 The most common radiological findings after aspiration of a foreign body in the lower airways (39,40)

Radiological finding	Mechanism
Hyperinflated lung (lucency distal to the obstruction)	This is caused by partial airway obstruction with air trapping, such that air passes with inspiration, but not with exhalation
Atelectasis	This is customarily caused by consummate obstruction of an airway, since air is resorbed from the distal alveoli over time
Mediastinal shift	The mediastinum inclines to shift away from the lung field containing the foreign body
Pneumonia	Infection often develops distal to an obstructed airway. Consequently, a consolidated infiltrate is withal a possible finding. Pulmonary abscesses and bronchiectasis are tardy manifestations of a retained airway FB

of the object is obscure (34).

Plain radiographic evaluation of the chest may or may not be helpful in establishing the diagnosis of FBA, depending upon whether the object is radio-opaque, and whether and to what degree airway obstruction is present. The diagnosis of FBA is readily established with plain radiographs when the object is radio-opaque (only about 10% of FBs). However, most objects aspirated by children are radiolucent (e.g., nuts, aliment particles) (35), and are not detected with standard radiographs unless aspiration is accompanied by airway obstruction or other complications (7,35-37). As a result, common findings on radiography do not rule out FBA, and the clinical history is the main determinant of whether to perform a bronchoscopy (38).

In children with lower airway FBA, the most prevalent radiographic findings are listed in *Table 3* (27,28,41,42).

The chest radiograph is normal in at least 30% of cases (7,41,43). The sensitivity of chest films has been reported to be between 68% and 76%, and the specificity between 45% and 67% when evaluating for FBs in the airway (44). Ideally, both inspiratory and expiratory radiographs should be obtained, if this is possible, because this may increase the sensitivity for detecting a radiolucent FB.

In adolescent children in whom it is arduous to obtain expiratory radiographs (either because they are tachypneic or because they cannot cooperate), left decubitus films may simulate expiratory radiographs. However, two retrospective studies suggested that these films did not integrate diagnostic value, at least as routinely performed (45,46).

If a laryngotracheal FB is suspected predicated on symptoms (stridor, wheeze, and dyspnoea, and sometimes hoarseness) a neck radiograph should be performed. These should include posteroanterior and lateral views, with the arms and shoulders situated inferiorly and posteriorly to optimize the image of the larynx and trachea. Even if the

FB is radiolucent, these films may suggest the diagnosis if they show a subglottic density or swelling (25).

CT is a possible diagnostic option for patients who are asymptomatic or symptomatic but stable, who have normal or inconclusive plain radiographs but a perpetual clinical suspicion of FB aspiration. However, this imaging is only subsidiary if the provider judges that negative imaging would be adequate to preclude bronchoscopy (47,48).

Treatment

An emergency endoscopy is obligatory in critical situations. After the patient is anaesthetised in recumbent position the neck should be gently extended. We advocate the use a laryngoscope to also inspect the larynx as part of the bronchoscopy.

The ventilating endoscope is than carefully introduced into the trachea, while ventilation continues. All air passages are carefully examined, and the FB abstracted through or with the bronchoscope.

FB extraction will fail with bad vision or sometimes when fragmented particles have moved more distally. These are sometimes amenable for extraction utilising a Fogarty catheter. In very rare cases more drastic procedures may be require such as bronchotomy or resection of the lung.

Corticosteroids or bronchodilators may be indicated to decrease oedema. Adrenaline can also be useful in certain circumstances. Chest radiographs are mandatory in the follow-up for the identification of pneumothorax and/or air in the mediastinum following FB extraction (4,26).

FB extraction

If FBA is known to have occurred or is vigorously suspected, rigid bronchoscopy is the procedure of choice to identify

and extract the object (29,34,49). Rigid bronchoscopy sanctions control of the airway, good visualization, manipulation of the object with a wide variety of forceps, and yare management of mucosal haemorrhage (20,50-52).

Bronchoscopy is successful in extracting the FB in approximately 95% of cases, with a very low complication rate of less than 1% (7,53,54). Thoracotomy is rarely indicated in those cases in which FBs can be visualized but cannot be extracted by means of a rigid bronchoscope.

FB extraction should be performed by an experienced operator to minimize the jeopardy of complications. Unsuccessful attempts to remove the FB may push it into a distal position, making them more arduous to retrieve. Disintegration or dislodgement of all or part of the FB, or a fragment of the FB, into the main bronchus of the contralateral lung are potentially lethal complications if the pristinely involved bronchus remains obstructed by inflammation or residual FB (55). Major complications of FB extraction include pneumothorax, hemorrhage, and respiratory apprehend, but they occur infrequently.

Alternatively, flexible (rather than rigid) bronchoscopy is utilized to extract the FB in some centers with experience in this technique (28,51,56,57). This technique customarily is circumscribed to older adolescents or adolescent adults. Potential advantages of utilizing flexible bronchoscopy for FB extraction are avoidance of general anaesthesia and the facility to reach sub-segmental bronchi.

In a large case series, the FB was successfully extracted by flexible bronchoscopy in 91% of patients (28). The main disadvantage of flexible bronchoscopy for FB abstraction is the peril of dislodging the FB and further compromising the airway. Because of these concerns, the American Thoracic Society (ATS) states, "*In general, rigid instruments are superior for detailed anatomic assessment of the larynx and cervical trachea and for operative manipulation, principally foreign body extraction*" (52). Flexible bronchoscopy is commonly utilized by most centers for management of FBA in adults.

If there is a suspicion for multiple diminutive FBs or fragments, we recommend performing a flexible bronchoscopy after FB abstraction, to evaluate the entire tracheobronchial tree (31,58).

Complications

When FBA is diagnosed soon after the event, there is customarily little damage to the airway or lung parenchyma. The longer the FB is retained, the more likely are complications (e.g., atelectasis, post-obstructive pneumonia). A FB that causes chronic or recurrent distal infection may lead to bronchiectasis (31,39,40,59,60). This complication should be treated after the FB is abstracted. Cultures obtained during bronchoscopy guide the initial antibiotic cull in treating infected areas of bronchiectasis. Failure to promptly diagnose the FBA may additionally cause complications from the utilization of non-indicated treatments, such as steroids, antibiotics, or bronchodilators (61,62).

Prevention

As a general rule, primary passive intervention strategies to reduce the jeopardy of FBA (e.g., legislation that eliminates choking hazards from the market) are more efficacious than active intervention strategies (strategies that require constant parental supervision) (63).

Materials and methods; experience of trauma unit in Red Cross War Memorial Children's Hospital, University of Cape Town

All data were recorded for every patient since 1991. All patients were treated according to the unit's management protocol (*Figure 2*).

Results

A total retrospective study was performed on 88,822 children who attended the trauma unit from January 1991 till December 2000. Fall from a height was the commonest trauma (n=32,766) 21%, transportation traumas (n=11,915) 13%, Burns (n=7,241) 8%, struck by objects (n=9,064) 10%, FBs (n=3,677) 4%, sharp objects (n=3,601) 4% and assault (n=3,302) 4% (*Figure 3*). Three-hundred and forty [340] patients were analysed in more detail.

Genders were similarly influenced. Ages went somewhere around 0 and 12 years, in spite of the fact that there was only one kid less than 1 year, at 2 years of age rate increased dramatically, with 25% of all cases happening (*Figure 4*).

Details of aspirated or ingested FBs

Most of them were of metallic nature (44%) or made of plastic (21%) (*Figure 5*).

Coins were the most common FB (30%), bead (8%) and pellet (7%), (*Figure 6*). Diameter was 0.1–3 cm.

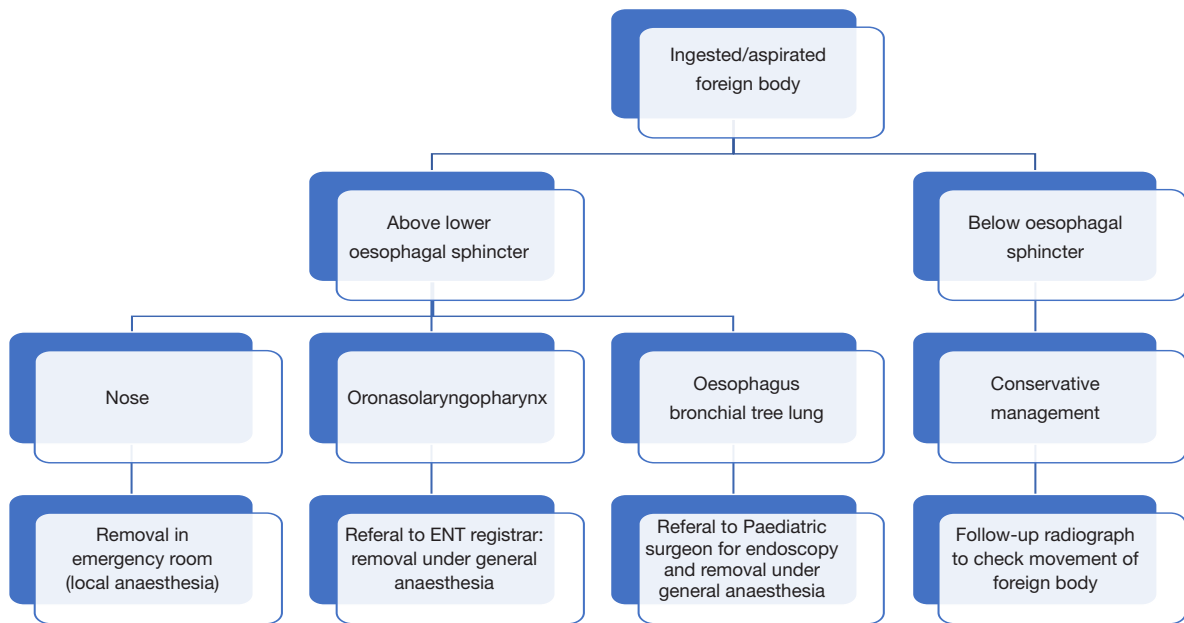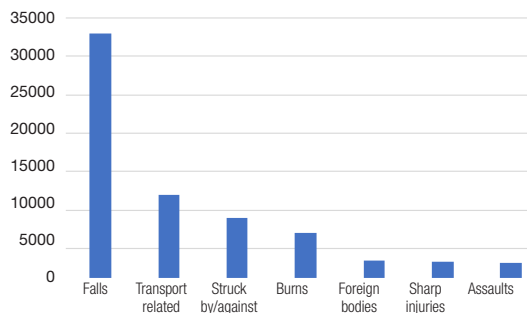**Figure 2** Management protocol of foreign bodies at the trauma unit.

Figure 3 Number of pediatric injuries from 1991 till 2000 (n=88,822).
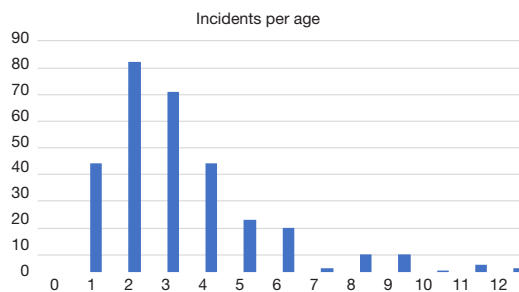

Figure 4 Number of foreign body aspiration or ingestion cases according to the ages of the children in years. FB, foreign body.
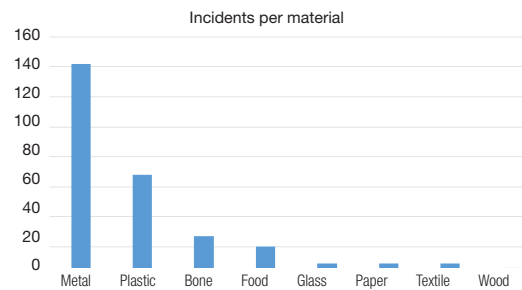

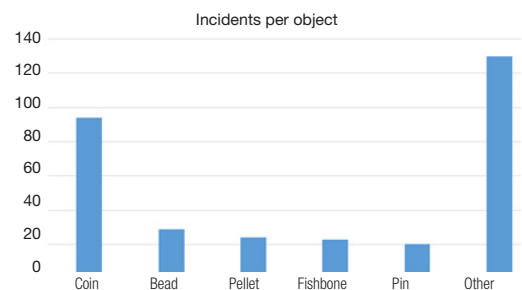**Figure 5** Material of FB. FB, foreign body.

Figure 6 Ingested or aspirated foreign body: nature of the aspirated foreign body.
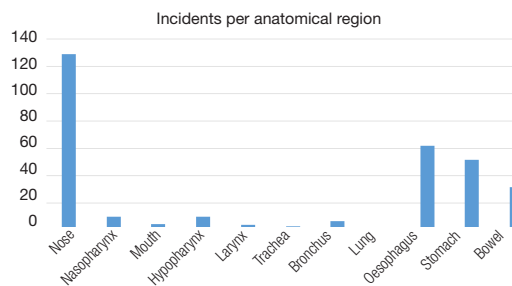
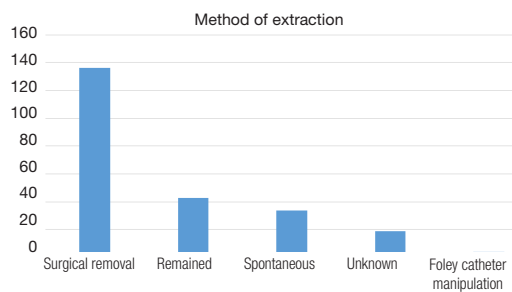**Figure 7** Ingested or aspirated foreign body: anatomical region of object.

Figure 8 Method of extraction of the foreign body.

Anatomical region affected

Nose (129 cases or 41%), followed by the oesophagus (64 cases or 20%), Stomach (52 cases or 17%) and bowel (32 cases or 10%). Other anatomical sites included nasopharynx (11 cases or 4%), Hypopharynx (10 cases or 3%), bronchus (6 cases or 2%), oral cavity (4 cases or 1.3%), larynx (3 cases or 1%), trachea (2 cases or 0.7%) and lung (1 case or 0.3%) (*Figure 7*).

Severity of symptoms

Case were rated utilising the Abbreviated Injury Score (AIS). We found that 0.6% of conditions were severe, 14% were moderate and 49% were mild. Thirty six percent was asymptomatic.

Retrieval of FBs

Fifty-seven per cent (57%) of FBs were extracted by surgical means, 19% left in place, 14% spontaneously came out and 1% extracted by Foley's catheter (*Figure 8*).

Regarding the most vulnerable age for aspiration, the difference according to sex was studied. Where girls are susceptible from an early age (3.0 years), they are only at

risk for a relatively brief period (3.0 to 3.9 years), a period of approximately 10 months (P=0.023). However, boys are susceptible at a later age (3.7 years), but remain at risk for a far longer duration (3.7 to 5.1 years) or a period of approximately 15 months.

Discussion

Trauma represents a very important part of mortality and morbidity worldwide with disregard to age and sex. Road traffic crashes, falls from heights and interpersonal violence are among the fundamental drivers of harm related disability and death (64).

Traditionally, trauma was viewed as unpreventable and only recently has been perceived as avoidable (65,66).

Childsafe South Africa's (CSA's) database was used as the fundamental hotspot for investigation of ingestion and aspiration trauma conditions experienced in Cape Town. Over the last 25 years we have been prospectively collecting data on all childhood injuries utilizing a constant data sheet.

There have been relatively few reports on FB ingestion and aspiration from Africa. Several reports indicate the predominance of peanuts as the aspirated FB (67,68). Where most reports indicate a low morbidity, some report a high mortality (11%) of children aspirating a FB (69). In Durban (South Africa), three children died after aspirating parts of a ballpoint pen (70).

There have been attempts to correlate the size of the ingested object with the anatomical location of impaction (71). Nearly all reports on FB ingestion show a predominance of boys (about two-thirds of all patients).

The presentation of a child with aspiration can vary greatly (e.g., in many series, less than 50% present with the history of aspiration) and the diagnosis might be difficult. However, most children present with coughing (approximately 80%), dyspnoea (approximately 70%), have abnormal auscultation (approximately 75%), or abnormal radiographs of the lateral cervical spine (soft tissue) or chest (approximately 60%).

FBs aspiration and ingestion is the fifth most common indication for admissions to our unit. In our review the rate of severe adverse outcome was very low (only 0.4%); this may be a result of transport issues in our environment. Seriously injured patients may have given up amid the long duration of transportation and we are currently gathering information on this issue.

Coins were the commonest ingested or aspirated FBs. It might be due to shortage of toys in our communities.

FBs lodged in the nose were more common than in the oesophagus. Most FBs were extracted in the operating room with the patient anaesthetized, by method for oesophagoscopy. FB's that either reached the stomach or were left alone and passed all through the GIT tract without further complications.

Although it is generally known that boys are at higher risk than girls, no detailed information is usually provided regarding prevention. An analysis was performed on the exact age for both sexes. Comparing the box and whisker diagrams of both sexes, there is a good overlap between the medians of both groups.

However, the 95% intervals calculated with the means indicate that there is a gap between the average ages of both groups susceptible for ingestion of FBs. Where girls are susceptible from an early age (3.0 years), they are only at risk for a shorter period (3.0 to 3.9 years), a period of approximately 10 months (P=0.023). However, boys are susceptible at a later age (3.7 years), but remain at risk for a far longer duration (3.7 to 5.1 years) or a period of approximately 15 months.

The results of this study confirm the frequent occurrence of FBs ingestion and aspiration in paediatrics and have implications for preventive measures. Parents of children should be educated about the specific period in which their child is most susceptible for the ingestion and aspiration of a FB, and preventive programmes should also be aimed at preschool children (e.g., minimising young children's access to metal coins).

Conclusions

Ingestion or aspiration of FBs is very common in paediatric age group. Coins were the commonest aspirated FBs in South Africa. On the premise of this study we firmly advice parents and caregivers to keep coins far from kids, particularly youngsters less than 6 years old. We used the results of this study in our programs for prevention.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Update in the extraction of airway foreign bodies in adults

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Abstract: Foreign body (FB) aspiration into the airway is lees common in adults than children. Nevertheless its incidence does not decrease through time. We present clinical relevant aspects of airway FBs on the basis of a selective review of pertinent literature retrieved by a search in the PubMed database. The most common aspirated FBs by adults are organics, especially fragments of bones and seeds. Symptoms usually are cough, chocking and dyspnea. Right localization, especially bronchus intermedius and right lower lobe, is more frequent. Chest radiography can be normal in up to 20% of the cases and FBs can be detected in 26% of the patients. FBs can safely remove in the majority of patients under flexible bronchoscopy. Surgical treatment must be reserved for cases in which bronchoscope fails or there are irreversible bronchial or lung complications.

Keywords: Bronchoaspiration; foreign body (FB); fibrobronchoscopy; rigid bronchoscopy

Introduction

Aspiration of a foreign body (FB) is a potentially life-threatening emergency and 75% of cases occur in children younger than 3 years of age (1-3). However, FB aspiration does happen in adults and elderly people as well (4). The estimated incidence in these age groups is not well known, but in literature is around 0.2% to 0.33% of all performed bronchoscopies (5-9).

The first published case of endoscopic extraction occurred on March 1897, when a German farmer experienced dyspnea, cough and hemoptysis after aspirating a pork bone. Using a modified Mikulicz-Rosenheim esophagoscope (a rigid tube illuminated with a mirror) and rigid forceps, Gustav Killian removed the splinter from de right main bronchus (10). Currently, both rigid and flexible bronchoscopes are performed for this indication depending on the age of the patient and the nature of the FB (5).

The aim of this review is to describe the clinical, radiological and endoscopic characteristics of adult patients with FB bronchoaspiration.

Methods

In order to compile this review article we conducted a selective literature search in PubMed (last accessed on 30 August 2016). A total of 125 manuscripts matched our search term "airway FB and adult NOT child NOT case report". Restricting the search to include only articles in English or Spanish reduced the number of matches to 95 articles. After excluding articles with case reports, with children or with fewer than 10 patients, we were left with 12 publications.

Because data from randomized studies are lacking, we based our article exclusively on retrospective publications, reviews, and recommendations from medical specialty

societies in patients older than 14 years old.

The analysed variables were: age, sex, clinical picture, risk factors for aspiration, type of FB, radiographic findings and information concerning the FB removal (type of bronchoscopy and surgical requirement).

Clinical presentation

Taking account all the selected papers, the mean age of patients with FB aspiration is 48 years with a range of 16 to 99 years. In all series, male sex is more frequent with a ratio 1.5:1.

The classical triad of cough, dyspnea, and cyanosis occurs in only a small percentage of patients (11). A non-asphyxiating FB may be asymptomatic, especially in elderly people. Many of these objects are wedged distally and patients often do not recall the choking episode, the aspiration, or any precipitating event (4). Thus, FB aspiration is commonly misdiagnosed. In some cases the delay in establishing the correct diagnosis and initiating the appropriate treatment after aspiration can be long periods of time, for months to years (6). Moreover, they often result from fortuitous discovery when fibrobronchoscopy is performed to evaluate a chronic cough, hemoptysis, or a slow resolution of pneumonia (7). In the analysed series the longest time between the bronchoaspiration and FB removal was 30 years (12). The most common symptoms of a nonasphyxiating FB reported were: cough (66.1%), choking (27%), dyspnea (26.6%), fever (22.2%) and hemoptysis (17.2%).

We have found that few papers report risk factors present in patients with airway FB. Nevertheless we think that it is an important fact because it helps us to understand the mechanism of bronchoaspiration and sometimes the type of FB aspirated (6). The most frequent risk factors are older age, abuse of sedative medications, neurological disorders, mental retardation, trauma with loss of consciousness, dental care, alcoholism and tracheostomy cannula handling (6,8,13).

FB aspiration in adult patients is more frequently in the right bronchial tree, this could be explained by a more direct pathway of the right main stem bronchus whereas in children right and left bronchial trees present an equal distribution (14,15). Analyzing all series, we have checked that FBs were more frequently in the right bronchial tree versus left bronchial tree (71.5% *vs.* 22.8%) and only 5.7% were in the trachea. Lodgement was more common in intermediaries bronchus (27%) and right lower lobe (33%).

Radiological findings

With regard to radiological findings, the standard posteroanterior or lateral chest X-ray is performed in almost all of the patients with suspected FB aspiration. There are few papers reporting the use of computed tomography (CT) to diagnose a FB aspiration (for example, 35% of the cases in the paper published by Hsu; they explain that CT was useful to plan the airway intervention) (8). It is striking the paper published by Lin *et al.* (4). They performed CT in 96% of the patients. This fact can be explained because they studied a geriatric series and symptoms were nonspecific.

Radiopaque FBs such as seen in *Figure 1* may be visualized in 26% of the cases. Metallic FBs are easily identified with great accuracy but they have a low frequency. In up to 20% of cases with suspected airway FB the chest X-ray can be normal. This fact should not obviate bronchoscopic evaluation in a clinical setting where the suspicion for airway FB aspiration is high (16). Delayed complications due to FB aspirations can result in recurrent pneumonia, obstructive emphysema, bronchial stenosis, bronchiectasis, pneumothorax, pneumomediastinum, recurrent hemoptysis, pleural effusion, empyema or bronchopleural fistula (17,18). Analysing all series, we observed the followed radiological findings: consolidation (43%), bronchiectasis (5%), and atelectasis (15%). Other signs like empyema, lung abscess, hyperinflation or pleural effusion were occasional (*Figure 1A,C*).

Categorizing foreign bodies

Airway FBs can be classified into organic and inorganic substances (17). After analyzing all papers, it seems sensible to relate FBs with the risk factors presented in patients. Thus, organic FBs group includes bone fragments (specially chicken), fishbones, pieces of vegetables or fruits (for example pit cherries or bone plumps) and seeds (melon, sunflower). These FBs are more frequent in older patients and alcoholism abuse (6). Inorganic FBs comprehend pins, screws, rivets or plastic devices. They are typical in young people that accidentally aspirate small plastic or metal objects that had been introduced into the mouth as entertainment. Inorganic group also includes teeth (prevalent in craneoencephalic traumatisms), tablets or hypodermic needles (typical in IV drug addiction). We also could include an iatrogenic subgroup that comprehends pieces of voice prosthesis, tracheostomy cleaning brushes or
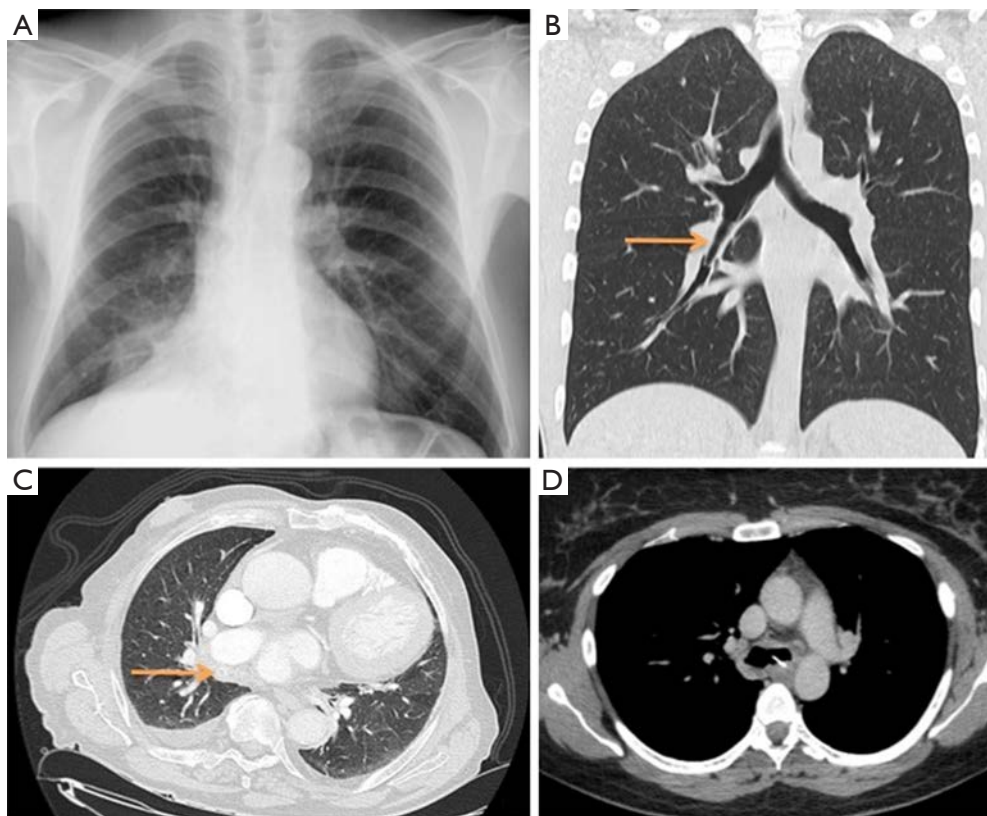
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Figure 1 Radiological images showing complications and/or different radiopaque foreign bodies. (A) Posteroanterior chest radiograph. We can observe a consolidation in the medium lobe caused by chicken bone; (B) coronal image of CT. Arrow is showing a Bic cap lodged in the bronchus intermedius; (C) axial image of CT. Right pleural effusion and a cherry pit indicated by arrow; (D) axial image of CT. We can observe a deer bone lodged in left main bronchus. CT, computed tomography.

dental bridges (*Figure 2*).

The most common group of FBs was the organic (47%; range 26–62%). In this group, the fragments of bones with a 20% stood out, followed by seeds (17%). Inorganic FBs counted 41% (range, 35–62%). The most frequent were tooth (10%) and metallic FBs (8%). In the iatrogenic subgroup any FB stands out of other representing a minimum percentage in each series.

FB removal

Although the rigid bronchoscope is still considered as the safest instrument in most pediatric centers to FB removal (11), most of the studies included in this review, considered the flexible bronchoscope as the initial and preferred method of choice to treat the adult airway (*Table 1*).

Flexible bronchoscopy is a relatively easy and safe procedure in experienced hands. With the use of a flexible bronchoscopy under local anesthesia to visualize airway,

removal of a FB can be attempted and avoids the added cost, risk, and morbidity of a secondary invasive procedure such as rigid bronchoscopy under general anaesthesia (22,23).

In our analysis, most of FBs were retrieved with flexible bronchoscopy, with a pooled success rate of 79.1%. Open surgical procedures were required for only 3.76% of the patients. In some series, surgery was necessary in more than 10% of the cases (6,12). Usually, these patients had residual lesions following inflammatory process (6).

Du Rand *et al.* removed FBs using a rigid bronchoscopy in 60% of the cases (22). However, in other papers like the reported by Hsu, the majority of FB removed by rigid bronchoscopy could not otherwise be done with flexible bronchoscopy. This is due to the fact that FBs were stents and its retrieval was only possible with rigid bronchoscopy (8).

The most useful instruments for FB removal are shark-tooth forceps, alligator forceps or wire basket (2,5,8). In some cases suction is enough to resolve the problem. Complications during bronchoscopy are very rare. Bleeding
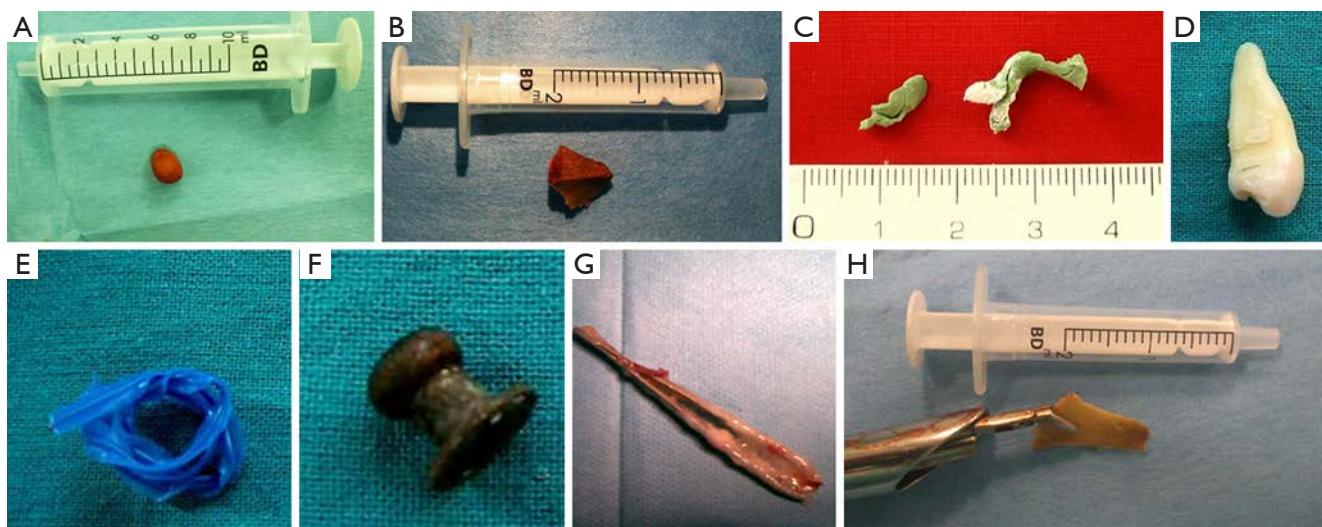
Figure 2 Different FBs removed by flexible or rigid bronchoscope. (A) Cherry pit from an older patient; (B) fragment of a pork bone; (C) bronchial mold made from synthetic material used to make a dental prosthesis; (D) a dental piece removed from a patient with craneoencephalic traumatism; (E) plastic device used to close some bags with manufactured products; (F) a rivet; (G) hair clip removed from a patient with tracheostomy; (H) deer bone lodged for two years in the airway. FB, foreign body.

Table 1 Cases series of airway FB removal

First author, year (reference)	Patients (n)	Method used for FB removal [n (%)]	Surgery [n (%)]
Limper, 1990 (19)	60	14 (23.3%) flexible bronchoscope; 37 (61.6%) rigid bronchoscope; 6 (10%) both	3 (5%)
Lan, 1994, (20)	47	41 (87.2%) flexible bronchoscope; 5 (10.6%) lost follow-up and spontaneous expulsion	1 (2.1%)
Chen, 1997 (12)	43	32 (74%) flexible bronchoscope; 2 (4.6%) rigid bronchoscope; 3 (7.5%) no dates	6 (13.9%)
Doñado, 1998 (13)	56	54 (96.4%) flexible bronchoscope; 2 (3.5%) rigid bronchoscope	1 (1.7%)
Debeljak, 1999 (5)	62	42 (68%) flexible bronchoscope; 4 (6%) rigid bronchoscope; 16 (26%) both	1 (1.6%)
Swanson, 2004 (16)	65	58 (89%) flexible bronchoscope; 2 (3.07%) rigid bronchoscope; 4 (6.3%) both	1 (1.56%)
Ramos, 2009 (6)	32	24 (75%) flexible bronchoscope; 4 (12.5%) rigid bronchoscope; 2 (6.3%) both; 2 (6.3%) spontaneous expulsion	5 (15.6%)
Mise, 2009 (7)	86	86 (100%) flexible bronchoscope	1 (1.16%)
Rodrigues, 2012 (21)	40	34 (85%) flexible bronchoscope; 6 (15%) rigid bronchoscope	1 (2.5%)
Lin, 20014 (4)	43	43 (100%) flexible bronchoscope	0
Sehgal, 2015 (9)	49	45 (91.8%) flexible bronchoscope; 2 (4.08%) rigid bronchoscope; 2 (4.08%) lost follow-up	0
Hsu, 2015 (8)	80	48 (60%) flexible bronchoscope; 32 (40%) rigid bronchoscope	0

FB, foreign body.

is the most frequent (1% of the cases). With regard to bronchoscopic findings due to FB impaction, the most common lesion is granulation tissue (43% of cases) and mucosal inflammation (28%).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Clinical analysis of eight patients with blunt main stem bronchial injuries

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Background: Blunt main stem bronchial injuries are rare but potentially life-threatening injuries in clinical. The aim of this study was to sum up the experience on diagnosis and treatment of blunt main stem bronchial injuries.

Methods: This report retrospective1y analyzed eight cases of main stem bronchial injuries induced by blunt chest trauma between 2013 and 2016 in Tangdu Hospital, Fourth Military Medical University.

Results: There were eight patients, including four men and four women. The definitive diagnosis was confirmed by fibrobronchoscopy. Mean time between injury and treatment in our hospital was 4.25 days (range, 1–12 days). Mean length of airway tear was 1.04 cm (range, 0.5–2 cm). In four patients there was an injury to the left main stem bronchus, in three patients to the right main stem bronchus and in one patient to the ambilateral main stem bronchus. Emergent operation was performed in two patients and elective operation in six patients. End to end bronchial anastomosis was performed via right thoracotomy in two patients and via left thoracotomy in three patients, and primary repair was performed via right thoracotomy in two patients and via left thoracotomy in the remaining one patient. There was no death in this group. Seven patients had no complications and were able to take part in normal activities. One patient suffered from anastomotic stricture after operation was healed by granulation tissue resection and cryotherapy under fibrobronchoscopy.

Conclusions: Fibrobronchoscopy is able to define the blunt main stem bronchial injuries precisely and surgical approach is the preferred method for patients with these life-threatening complications.

Keywords: Main bronchus; blunt injury; fibrobronchoscopy; surgery

Introduction

Blunt main stem bronchial injuries are rare but potentially life-threatening injuries which can caused by a great diversity of direct or indirect traumas. Karmy-Jones investigated 1,178 patients dying due to blunt trauma and only 33 (2.8%) developed a blunt main stem bronchial injury (1). Most of the patients die at the site of injury due to asphyxia, which associated with a high mortality of 30% and early intervention is the key to survival (2). Trauma history is the premise for correct diagnosis of blunt main stem bronchial injuries and special clinical sign, such as pneumoderma in the neck and chest, pneumomediastinum, pneumothorax can give invaluable clues to the diagnosis. Conventional radiology tests such as X-ray and computed

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Table 1 Clinical characteristics of the eight patients with blunt main stem bronchial injuries

Patients	Sex	Age (years)	Position of injury	Length of injury (cm)	Inpatient days
Patient 1	F	42	Right	0.6	37
Patient 2	F	31	Right and left	2	27
Patient 3	F	14	Left	1	12
Patient 4	F	43	Right	0.5	14
Patient 5	M	28	Left	0.5	27
Patient 6	M	20	Left	2	18
Patient 7	M	17	Left	0.8	18
Patient 8	M	32	Right	2	12

tomography (CT) are useful of primary diagnostic tools in initial trauma examination (3). Bronchoscopy is crucial to the precise diagnosis of blunt main stem bronchial injuries in a patient with suspected airway injury, which can show the detail of injury, such as size, site and extent (4). The first and most important priority in blunt main stem bronchial injuries is to ensure adequate airway, and surgical approach is the preferred method for ventilation reestablishment.

Methods

This report retrospective1y analyzed eight cases of main stem bronchial injuries induced by blunt chest trauma between 2013 and 2016 in Tangdu Hospital, Fourth Military Medical University.

Results

Characteristics of the study group

In the analyzed group, eight patients were diagnosed with blunt main stem bronchial injuries and treated by surgery. There were four women patients (50%) and four men patients (50%) with the mean age of 28.4 years (ranging from 14 to 43 years). In four patients there was an injury to the left main stem bronchus, in three patients to the right main stem bronchus and in one patient to the ambilateral main stem bronchus (*Table 1*).

Diagnose of the injuries

All patients were admitted to our hospital from peripheral hospital with history of blunt chest trauma. One patient was intubated with single lumen endotracheal tube. Mean time between injury and treatment in our hospital was 4.25 days

(range, 1–12 days).

The most frequent sign was chest pain, followed by pneumoderm in the neck and chest, respiratory distress, dyspnea and haemoptysis. In all cases chest X-ray and CT were gained on emergency ward to check for subcutaneous emphysema, pneumothorax, pneumomediastinum and pulmonary atelectasis, as well as to obtain more details on anatomy (*Figure 1*). Moreover, fiber-optic bronchoscopy was done with investigation of the size, site and extent of lesion on emergency ward or on operating room (*Figure 2*). Mean size of airway injury was 1.04 cm (range, 0.5–2 cm). Oesophagoscopy was also applied to exclude esophageal rupture, esophagotracheal fistula, and so on.

Treatment of the injuries

Emergent operation was performed in two patients and elective operation in six patients. The principle of surgical treatment is that interrupted primary repair with PDS 4-0 was adopted in cases with simple clean main stem bronchial injuries and debridement of devitalized tissue including granulation tissue and cartilage, end to end anastomosis with absorbable sutures was performed in cases with serious tainted damage (*Figure 3*). In our group, the primary repair was performed via right thoracotomy in two patients and via left thoracotomy in one patient, and the end to end bronchial anastomosis was performed via right thoracotomy in two patients and via left thoracotomy in the remaining three patients. In one case the anastomotic stoma was additionally covered with a pericardium. There was no air leakage through the anastomosis site at positive pressure of 30 cmH$_2$O. Closed drainage of pleural cavity and posterior mediastinum drainage were routinely performed. After operation, all the patients were transferred to the intensive
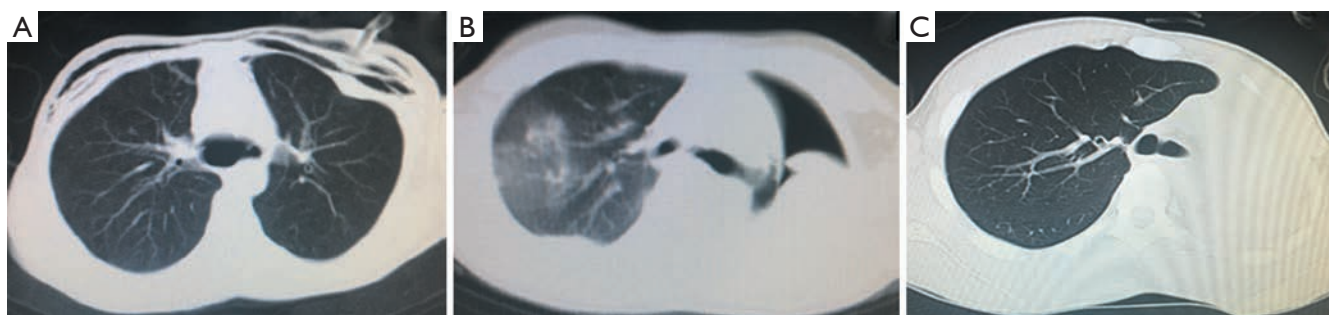
Figure 1 The most common CT characteristics of blunt main stem bronchial injuries were subcutaneous emphysema (A), pneumothorax (B) and pulmonary atelectasis (C).
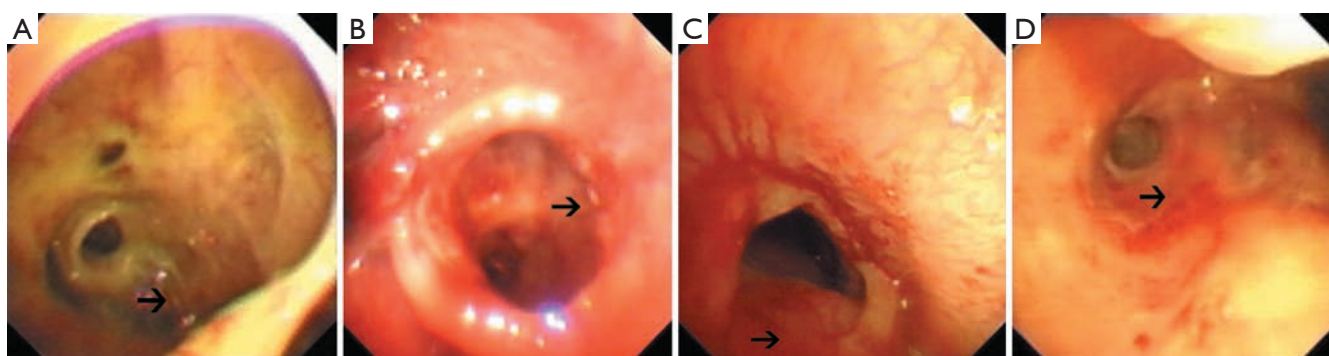

Figure 2 Fibrobronchoscopy provides the site, size, and extends of injury (Black arrow) in right main bronchus (A,B) and in left main bronchus (C,D).

care unit (ICU), and fibrobronchoscopy was performed routinely so as to clear bronchial secretions and check integrity of anastomotic stoma. Additional, intravenous antibiotics and aerosol inhalation mucolytic agent were administered. The average hospitalization time was 20.63 days (range, 12–37 days).

There was no death in this group. Arterial blood gases after bronchial repair showed markedly improved. One patient with left main stem bronchi injury developed anastomotic stricture 1 month after surgery, and was healed by granulation tissue resection and cryotherapy under fibrobronchoscopy. No main stem bronchus injury-related complications were noted in the remaining seven patients and they were able to take part in normal activities (*Figure 4*). The follow-up fibrobronchoscopy was performed at 3 months after surgery which confirmed complete healing and good patency of the airway in all patients.

Discussion

Main stem bronchial injury occurring after blunt trauma is

a rare scenario that requires skillful handling of airway (5). The reported incidence in literature is less than 2.8% (1,6). While it is a highly lethal cause of asphyxia at the moment of injury, and universally fatal in misdiagnosed patients or in incorrect managed cases with a high rate of mortality. Here, we report a series of eight cases of blunt main stem bronchial injury with good results.

Blunt main stem bronchial injuries can caused by a great diversity of direct or indirect traumas. However, the exact mechanisms of blunt main stem bronchial injuries have not heretofore been elucidated. Three theories have been reported account for the mechanism of blunt main stem bronchial injuries (7). One is the shearing force increased at the cricoids cartilage and carina. Second one involves the development of tensile force due to anteroposterior compression of the chest. The third one theory relates to the reflex closure of glottis while intrathoracic pressure rising suddenly. This leads to a rapid increase in airway pressure, especially in the ambilateral main stem bronchus. As the left main stem bronchus is fixed and protected by adjacent major vessels, while the right main stem bronchus
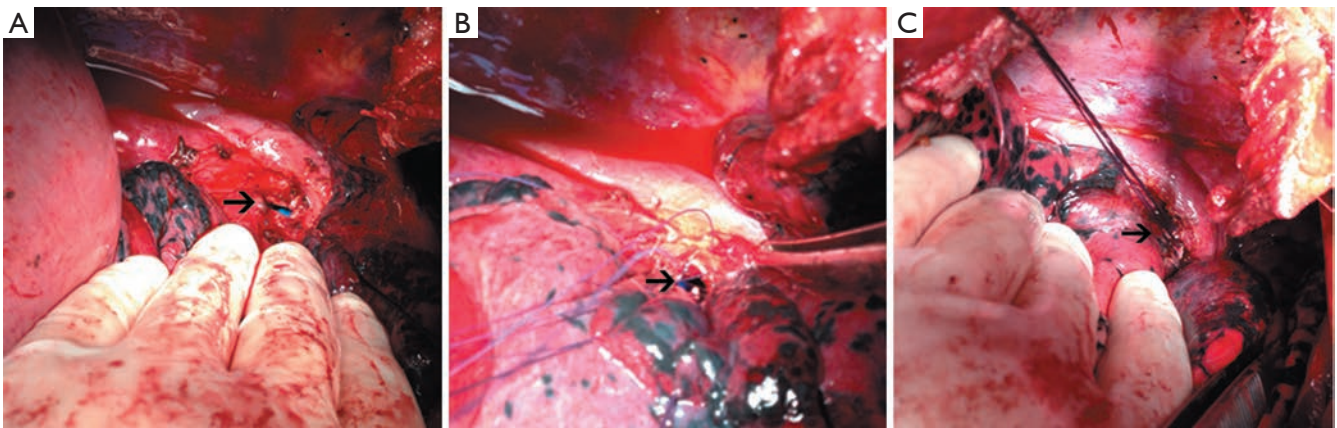
Figure 3 Primary repair was performed in patient with fresh and clean lesions (black arrow: lesion; A, before the repair; B, in the repair; C, after the repair).
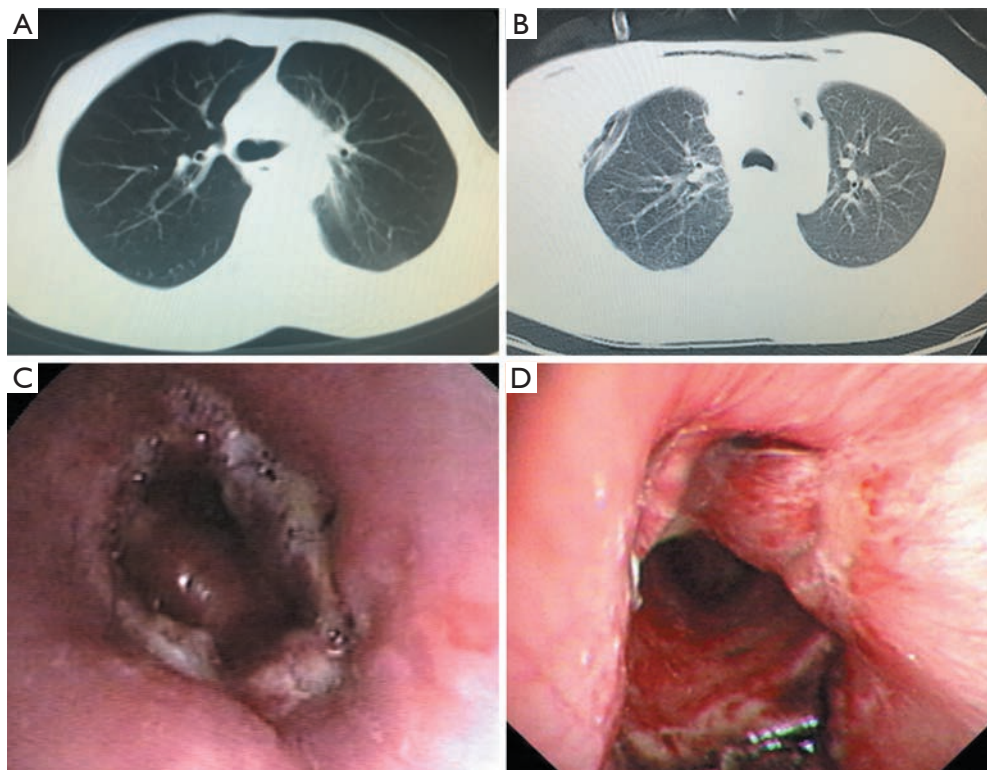
Figure 4 The postoperative chest CT and fibrobronchoscopy revealed that anastomotic stomas healing well in the left main stem bronchi (A,C) and in the right main stem bronchi (B,D).

lack of supporting structures and heavier right lung on the shorter right bronchus, more right main stem bronchus injuries been found. Nevertheless, in our patients only 3 out of 8 patients (37.5%) suffered from right main stem bronchus injuries, while 4 out of 8 patients (50%) suffered from left main stem bronchus injuries. Most of our patients

(50%) suffered from left chest trauma may account for the difference.

Make a diagnosis of blunt main stem injuries immediately is difficult. It was reported that blunt main stem bronchus injuries are not diagnosed immediately in 25% to 68% of the cases (8). The clinical manifestations are non-specific

and can vary from chest pain, cough, respiratory distress, dyspnea, haemoptysis to mediastinal emphysema, subcutaneous emphysema or pneumothorax (9). Almost all of the patients suffered from chest pain. Furthermore, subcutaneous emphysema, respiratory distress and dyspnea are frequent clinical features occurring in 77–85% of the patients (10). A massive air leak and the inability to re-expand the lung after tube thoracotomy are highly indicative of a main stem bronchus injury which was also seen in 4 of our patients (11). Additional, in our patients, eight cases complained of chest pain, six cases complained of respiratory distress, four cases with subcutaneous emphysema in the neck and chest, 1cases with haemoptysis.

Routine radiological tests such as X-ray and CT are extremely important in the early diagnosis of main stem bronchial injuries. Moreover, thorax CT maintains its effectiveness in inspecting trauma and it is availability in detecting the appearance of possible great vessel injuries, hemopericardium or mediastinal hematoma (12). It may show pneumoderm, pneumomediastinum, pneumothorax, pulmonary atelectasis, respiratory tree deviation or specific site of the separation. Complete disconnection of the main stem bronchi may make for the typical findings of atelectasis, "absent hilum" or collapsing of the lung away from the hilum towards to diaphragm is the classic imaging manifestations features of main stem bronchus injuries and known as "falling lung sign of Kumpe" (13). Pneumothorax, especially intractable pneumothorax with prolonged air leakage, should increase the suspicion of main stem bronchial injuries. Fibrobronchoscopy provides the resultful precise diagnostic study in a patient with suspected main stem bronchus injuries. The advantages of fibrobronchoscopy are that it can be performed quickly and easily even in the accompanying multi-organ injuries. Additional, it can be applied securely in the operating room with general anesthesia before operation. Check and examine the tracheobronchial tree carefully with fiber-optic bronchoscopy reveals the detail of injury, such as size, site and extent. Moreover, it is important that if fibrobronchoscopy is to be performed in an intubated patient, the endotracheal tube should be withdrawn carefully in order not to miss out small injury and proximal airway injury. In our patients, the thorax CT was performed in the emergency ward that provides useful clues for suspected main stem bronchial injuries. The definitive diagnosis of main stem injuries was confirmed by fibrobronchoscopy in endoscope room or in operating room, which provides the site, size, and extent of injury accurately.

Surgical treatment of the injuries of main stem bronchus can be extremely challenging. In patients, who cannot be managed conservatively, the most optimal therapeutic strategy is the surgical treatment as early as possible. Even in some minor injuries patients, granulation and structure may develop around the injuries; surgery also is the preferred method. The mortality for those who underwent primary repair was lower than those who underwent resection of the injured bronchus and distal lung parenchyma (3% *vs.* 13%) (8). In our patients, all the eight cases adopted the surgical therapy, and no one died during the perioperative period. Among them, emergent operation was performed in two patients and elective operation in the remaining six patients.

The right main stem bronchus, right atrium, superior vena cava, azygos vein and most of intrathoracic esophagus can be easily displayed by a right thoracotomy, while the left mainstem bronchi, descending thoracic aorta, distal part of aortic arch and proximal left subclavian artery can be easily exposure by a left thoracotomy. In our patients, four patients with left main stem bronchi injuries underwent left posterolateral thoracotomy through the fifth intercostal space, while the remaining four patients underwent right posterolateral thoracotomy, also through the fifth intercostal space. The principle of surgical treatment is that interrupted primary repair with PDS 4-0 was adopted in cases with simple clean main stem bronchial injuries and debridement of devitalized tissue including granulation tissue and cartilage, end to end anastomosis with absorbable sutures was performed in cases with serious tainted damage. Moreover, in cases with serious ambilateral main stem bronchial damage, all devitalized tissue should be debrided with the attention of preserving as much viable airway as possible (14). In our patients, end to end bronchial anastomosis was performed in five patients and primary repair in the remaining three patients. Primary repair was performed in three patients for their fresh and clean lesions. Meanwhile, for the late diagnosis patients, the optimal surgical treatment strategy is bronchial resection with reconstruction except the patients with unreconstructable lesions or destructed distal lung. It is noteworthy that appropriate seam of absorbable interrupted sutures assures airtight anastomosis and eliminates the discrepancy between the distal and proximal bronchus. It also ensures minimal anastomotic granulations. In our patients, there was no death under perioperative. Two emergency surgeries were necessary owing to worsening oxygen saturation, pneumothorax, and hemodynamics. It is encouraging that no pneumonectomy was performed in our group, even in

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the patient with ambilateral main stem bronchial injuries.

Blunt main stem bronchial injuries are rare but potentially life-threatening injuries. Early diagnosis and early surgical treatment are crucial to reducing death rate. Fibrobronchoscopy is the optimized diagnostic tool and surgical approach is the preferred method for patients with these life-threatening complications.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Ethics Committee of Tangdu Hospital (No. 201647).

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Update on the diagnosis and treatment of tracheal and bronchial injury

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Abstract: Tracheal and bronchial injury, including iatrogenic injury and traumatic injury, the former usually occurred in the operation, intubation or bronchoscopy. The latter was occurred in a variety of blunt trauma, often combined with a variety of complex injuries. The therapeutic approach can be differentiated, surgical or conservative, no criteria has been universally accepted. Successful treatment of tracheobronchial injuries requires early diagnostic evaluation. This article aims to review the indications and therapeutic options for tracheal and bronchial injuries.

Keywords: Tracheal injury; bronchial injury; diagnosis; treatment

Introduction

Tracheal and bronchial injuries are more common in patients with thoracic trauma caused by traffic accidents. However, with the development of medical treatment, iatrogenic injury is gradually increasing. Main treatment of trachea is kposthesis and anastomosis. So early diagnosis and early surgical repair are the key to reduce complications and avoid the loss of lung function in patients with tracheal and bronchial injuries.

Classification

From etiology the tracheobronchial injury can be classified as traumatic and iatrogenic sources, in which the traumatic etiology includes crush injury, firearm injury and sharp instrument injury, which can be combined with the injury of cervical and thoracic vertebrae, large vessel, lung, thyroid, heart, esophagus and so on; From mechanism it can be classified as blunt injury and sharp injury, and the blunt injury is frequently complicated by neck and chest combined injury, even severe throat edema that can result in asphyxia or pulmonary edema which can lead to respiratory distress syndrome. From the lesion site, it can be divided into cervical tracheal injury, thoracic tracheal injury, major bronchial injury and lobar/segmental bronchial injury.

Clinical manifestation

The clinical symptoms of simple airway mucosal laceration are always not obvious or only have small amount of blood sputum. It suggests presence of serious tracheobronchial injury with symptoms of shortness of breath, cyanosis, irritating cough, hemoptysis and pneumothorax. In severe chest trauma caused by traffic accidents or falling from height, the shear strain on the main bronchus caused by variable motion and the airway pressure surge caused by closed glottis can lead to rupture of the trachea and bronchi. Palade E reported that the right main bronchial rupture (47%) is more common than that in the left side (32%) for

the right main bronchus is more fixed. Main tracheal rupture accounts for 19% (1) (*Figure 1*). But Siegel *et al.* found that there was no significant difference in the incidence of injury between the left and right sides (2) (*Table 1*).

Dyspnea: there are many reasons that can cause dyspnea in tracheal rupture, such as pneumothorax, obstruction of blood or secretions in respiratory tract, pulmonary contusion that leads to oxygen exchange barriers, bronchial mucosal edema, hematoma compression to airway or lung tissue. The first symptom of main bronchial injury is pneumothorax, which often cause serious lung compression and even tension pneumothorax. As a result it blocks venous blood flow and results in heart failure, etc. (3). What's more, even after placing pleural closed drainage, large amount of gas can be drained out with the movement of respiratory. Refractory pneumothorax and long-term pulmonary
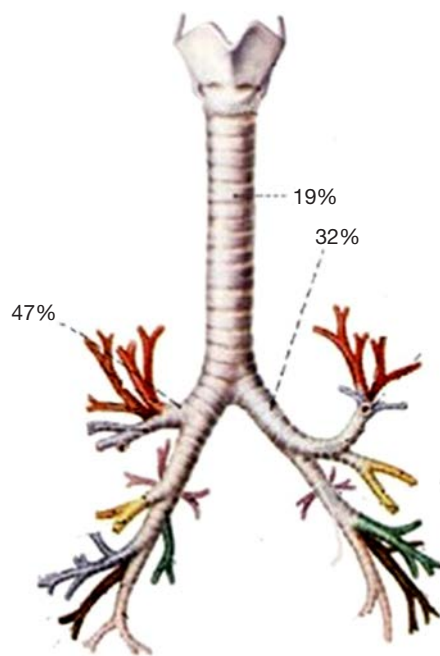
rehabilitation difficulty can also exist. The old tracheal injury can cause lobar or segmental atelectasis because of the granuloma in the lesion, so that it can present with symptoms like breathing difficulty and so on. However, the patients above always perform as recurrent pulmonary infection which is the main reason to hospital.

Subcutaneous or mediastinal emphysema: subcutaneous or mediastinal emphysema are the main symptoms of airway perforation with hemoptysis and dyspnea or not. Severe pneumomediastinum always appears in intrathoracic trachea injury, and the air can spread to the neck, head and chest, bilateral chest wall through suprasternal fossa that results in subcutaneous emphysema last. There are reports that the serious subcutaneous emphysema after trachea injury could even spread to the abdomen, perineum and lower extremity skin (4). In some cases the subcutaneous emphysema could also induce air embolism, but these patients were always associated with complex trauma and large vessel rupture etc. The severe pneumomediastinum might also compress the vena cava that led to reflux disorder and even heart failure.

Most of the hemoptysis caused by tracheal injury is slight, but it can also present with massive hemoptysis if there is bronchial artery injury or tracheal fistula with high mortality (5). Always there is fatal injury in these patients that will die from hemorrhagic shock and suffocation in short time, so that these patients have not enough time to be sent to the emergency room.

There is still a high misdiagnosis rate (68–35%) in the patients with mediastinal infection, bronchial pleural fistula, pulmonary atelectasis and injury of trachea and bronchus (6). And some patients were diagnosed until presenting with mediastinal infection and persistent pulmonary atelectasis.

Iatrogenic injury: the main symptoms of superficial injury are small hemoptysis, while the large damage can cause mediastinal or subcutaneous emphysema. Patients with ventilator support can occur with sudden lower airway pressure or tension pneumothorax. Such injuries are common in clinical practice, most of which occur in the

Figure 1 Tracheobronchial injury incidence of different parts.

Table 1 Incidence of different parts in different reports

Authors	No. of patients	Main tracheal rupture [%]	left main bronchial rupture [%]	right main bronchial rupture [%]
Palade (1)	265	50 [19]	84 [32]	124 [47]
Siegel (2)	88	14 [16]	34 [38]	40 [45]
Cheaito (3)	24	16 [67]	2 [8]	4 [17]
Szmygin-Milanowska (4)	119	12 [10]	29 [24]	78 [66]

Figure 2 Performance under the bronchoscopy of right bronchial rupture.

operation of tracheotomy (0.2%), tracheal intubation (0.1%) and esophageal surgery (0.4%) (7). It is difficult to find the mild injury which may even be delayed into a chronic airway injury and be found until the airway stenosis exist.

Diagnosis of tracheal injury

It is not difficult to diagnose the cervical tracheal injury with clear history of injury and wound sucking sound associated with respiratory movement. But the injury of thoracic trachea and bronchus are often overlooked. Barrett *et al.* believed that: the tracheal injury should be excluded in chest closed injury patients in spite of pneumothorax, especially in severe crush injury, blast injury or falling injury patients (8).

Examination means includes chest X-ray, chest CT and bronchoscopy. X-ray examination is simple and fast with clear diagnosis for complete rupture of the trachea. The "lung fall syndrome" always prompts the loss of bronchial suspension so that the injured lung decreases to the cardio-diaphragmatic angle, which is different from the compression of normal lung tissue to the hilum of lung for pneumothorax. The main tracheal rupture can also present with this decline for gravity which can be diagnosed with the tracheal disruption that could be performs on the chest X-ray.

Chest CT is better than chest radiograph in the diagnosis of the rupture of main bronchus or lobe/segment bronchus. The characteristic expression of tracheal rupture in CT performs as follows: (I) gas dispersion around the broken ends (59%); (II) bronchial lumen stenosis or blockage (50%); (III) bronchial displacement or angular deformity (50%) (9). The chest CT of the patients with chronic bronchial injury can be manifested as capsular bag change in the end of the proximal rupture, or local tubal wall stenosis with corresponding distal pulmonary atelectasis. But some

researchers believe that the diagnostic value of CT scan is not better than the chest X-ray, because tracheal fracture is always accompanied by multiple contusion, edema, hemorrhage or bronchial secretions blocking the lumen in the mediastinum and pulmonary, so that it is difficult to clearly determine whether there is tracheal injury by CT (10). For patients who cannot tolerate bronchoscopy, we can choose multi-planar two-dimensional or three-dimensional reconstruction and simulation bronchoscopy technology which can show the airway disease in conventional axial CT imaging in just a few minutes. For cases with severe chest trauma whose CT is negative but highly suspected bronchial rupture, the technique of three-dimensional reconstruction of MDCT can be used to reconstruct the bronchial tree for the diagnose of complete bronchus rupture.

Bronchoscopy is one of the diagnosis methods under which we can find the tube wall rupture (*Figure 2*), and it is better than the former above in the diagnose of small injury (11). Bronchus injury with unobvious symptoms can be found through this technique. At the same time, bronchoscopy can be used to accurately locate and estimate the degree/scope of damage so as to guide the treatment. Wood *et al.* suggested that it was necessary to use conventional bronchoscopy for trauma patients with high suspicion of bronchial rupture as soon as possible if patients' general status was available (12).

Tracheography can also be used in the diagnosis of tracheal injury, which is always used in patients with chronic bronchial injury or tracheal stenosis, especially in patients with trachea-esophageal fistula and trachea-pleural fistula.

Tracheography can also be used to distinguish the bronchial dilation or bronchial foreign body and chronic airway injury which is difficult to be identified by CT. In addition, because granulation tissue hyperplasia can lead to stenosis which provides blurred vision under bronchoscopy, so the tracheography has more diagnostic advantage (13). However, it is higher for the requirement of coordination degree in tracheography, so it is not suitable for patients with acute injury accompanied with hemoptysis, pulmonary atelectasis and bad general conditions.

Treatment of tracheal injury

Conservative treatment

The simple airway mucosal tearing is always self-limited without any special treatment. Cui *et al.* believed that if the breach was less than 1 cm, it could gradually stop leaking
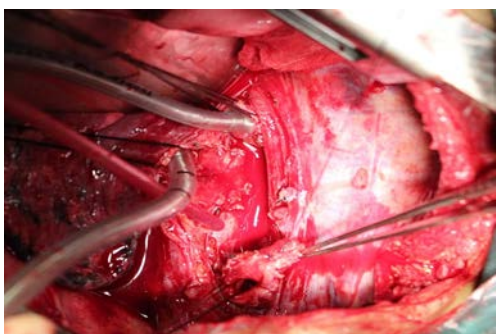
Figure 3 Intraoperative exploration of bronchial injury: prepare for end to end anastomosis.

and naturally be cured (14). Most scholars thought that simply small crack could be treated conservatively (15). The indications of conservative treatment: (I) <2–3 cm or <1/3 diameter; (II) no other injury (such as esophagus), mild symptoms and signs, no signs of infection, stable and patency airway, stable spontaneous breathing; (III) intrathoracic trachea-bronchial injury without persistent air leakage or reexpansion of the lung after chest tube drainage. In addition to the use of antibiotics to prevent infection, combination of closed thoracic drainage and negative pressure suction is also necessary. It can not only promote the ipsilateral lung reexpansion, but also absorb the surrounding tissue to pack the crack. The size of crack determines the degree of negative pressure. The larger gap requires the larger negative pressure to ensure the lung reexpansion. There were reports that suction with large negative pressure could be used for the treatment of bronchial rupture whose diameter was about 1.4 cm (16).

Emergency treatment

Most airway rupture is urgent and the patients are always sent to the emergency department. In the emergency treatment, airway patency should be the first step, we should clear the secretions in airway to ensure the supply of oxygen. If patients are in acute stage with severe air leakage, breathing difficulties and unstable general condition, they should be intubated after making a definite diagnosis. Intubation can also support the collapsed trachea (17). What's more, sometimes tracheal intubation can also play a role in temporarily blocking the tracheal rupture by breaking over the crack in the cervical or upper thoracic tracheal injury. For the patients with injury of inferior segment or bronchus, the cannula can be placed to the contralateral

main bronchus for one-lung ventilation, and the operation had better be finished under the guide of flexible bronchofiberscope to avoid aggravating the injury (18). It is better to avoid the positive pressure ventilation to prevent further expansion of tear as far as possible. The cannula can be placed in the subglottis with high frequency ventilation, which helps to prevent rupture from further expanding; it needs emergency thoracotomy surgery for the patients with difficult intubation or difficult ventilation. Cannula could be placed into the contralateral main bronchus by the guide of operator's finger. In recent years, the cardiopulmonary bypass (ECMO) was also used for the patients with difficult intubation to ensure the oxygen saturation (19). This method can be applied to the tracheal operation with wide range of crack which is difficult to repair. Patients with complete tracheal rupture caused by penetrating injury in the neck can also be directly rescued by intubating through the open wound in an emergency. In addition, the chest or mediastinal decompression is also very important in emergency treatment, and pleural closed drainage is often the preferred method (20).

Surgical treatment

In principle, rupture of the trachea and bronchus should be operated as soon as possible. The achievement ratio is very high in early repair on healthy tissue with quick improvement to the dysfunction of ventilation and better long-term outcome (21); the broken end delayed to late stage may appear scar stricture, infection, retraction and adhesion, which is not conducive to surgical repair. General surgery includes repair, end to end anastomosis, sleeve resection, lobectomy or pneumonectomy, autologous tissue repair or reconstruction (*Figure 3*). Most cases can be cured by repair or anastomosis. In addition to patients with severe pulmonary parenchymal injury, there is no need for lung resection. The unilateral whole pulmonary atelectasis caused by old main bronchial rupture can be reexpanded through tracheal intubation after removing lumen secretions in the airway. The combined injury should be repaired at the same time. Especially in patients with esophageal laceration, we can use adjacent healthy tissue or greater omentum to cover the laceration while repairing it (22).

Selection of operative incision

If the injury occurs in the proximal 2/3 trachea, the incision could be selected on the neck. When the trauma is mild and complication is little, we can use local anesthesia. At first, a

curved incision was made on the sternal notch with a cross finger. Then reveal the trachea by separating the anterior cervical muscle. If it is difficult to expose, we can do part or whole sternotomy (23). When the fracture occurs on the lower section of the sternum or main bronchus, incision could be selected on the posterior lateral right side. Then cut off the azygos vein to expose the trachea and carina. We can also select middle chest incision, so that there is no need to enter the pleural cavity with less impact on the breath and better postoperative recovery (24). However, thoracotomy is suggested to the patients with blunt injury or hemopneumothorax so as to detect the pleural hemorrhage and fracture, etc. (25).

Exploration

The neck injury or perforation is more common in the injury of neck. Injury site always located in the sagittal plane of trachea or the junction of cartilage and membranous part, which is close to the hematoma. Thoracic crack can be identified by pneumomediastinum or gas leakage. Most injuries (80%) locate in the carina within 2.5 cm (26). There were reports that tracheal injury can be complicated with cardiac vascular injury (27). Therefore, it is necessary to explore the major vessels of the heart in patients with severe injury. When there is obvious infection or putrid flavor, we need to focus on exploring the esophageal injury (28).

End to end anastomosis

After a thorough debridement and hemostasis, the edge of the gap should be trimmed to guarantee the wound end to end alignment, then the whole layer of the bronchial gap should be sutured. If the tension of the broken end is too high, the gap could be sutured with thick seam to hang together to reduce the tension, and the remaining is closed with a U type or interrupted suture from membranous part to the front line. The sutures should be kept outside of the lumen so as to avoid the postoperative irritating cough and the stenosis from granulation tissue hyperplasia. When the main airway injury is serious enough to make the upper and lower ends far apart, the neck can be fixed in 35 degree flexion with Pearson position to reduce the tension of the airway. Some studies found that the maximum distance of the main airway relaxation was 4.5 cm (29). When the difference of the diameter from the upper end to the lower end is big enough, the needle should be arranged evenly and sometimes one side could be cut off to expand the incision, or using the membranous part for correction. The needle had better go through the cartilage as far as possible, and the first

suture should be made on the difficult exposed part. The worked trachea should be avoided form tension, distortion and angle. After all of these above, it is better to cover the pleural flap or the muscle flap on the anastomotic stoma.

Lobectomy and pneumonectomy

Whenever possible, use bronchial rupture repair and anastomosis, and try the best to protect the lung tissue. We'd better avoid using lung resection, especially the whole lung resection which will significantly improve the postoperative mortality rate (30). But for the patients with serious lung damage that can not be repaired and prone to infection after operation, removal of the damaged lung is a necessary way for saving life. What's more, if the scope of the tracheal injury is wide enough that makes the operation more difficult and tends to postoperative tracheal stenosis, it is recommended to remove lung disease if the residual lung injury allows (26).

Chronic tracheal rupture

Stenosis always appears in chronic tracheal rupture due to the growth of granulation tissue or scar which should be resected and coincided in surgery. When the stenosis length is too large to cause high anastomotic tension, neck fixation could be used for relaxing and coinciding within 4.5 cm resection. If the distance is more than 4.5 cm, 3 cm distance could be prolonged through loosing and separating the upper and lower ends, separating the structure around hilum and loosing the explant adhesion.

Grillo *et al.* thought that prolonged distance could be finished through loosing inferior pulmonary ligament, separating large vessels and accretio cordis, and cutting off the left main bronchus and transplanting to the right main middle section in some special circumstances (31). The total length of trachea resection can be as long as 6.6 cm. One side whole pulmonary atelectasis caused by chronic main bronchial rupture can be well reexpanded by removing the airway secretions and using intubation ventilation. It has been reported that even the history of chronic tracheal injury was more than 2 years, the function of the distant lung could be recovered after surgery (32).

Postoperative treatment

After surgery, the lower jaw should be fixed to the skin of frontier chest with a thick line, so that the neck is positioned in Pearson position from which it can prevent the postoperative neck from suddenly moving back again

to break the not yet healed wound. The suture should be reserved for about 1 week until the breach has healed. The neck can be free after 2 weeks. But some scholars believed that the neck should be fixed for one month to prevent tracheal anastomotic stenosis (33).

The intubation can be removed after surgery. Patients complicated with pulmonary contusion should be kept intubation with the support of ventilation. We should pay attention to the position of the air bag that might be moved to the anastomotic site, because even the low pressure air bag will also affect the healing of tracheal anastomotic site (34).

After surgery we should remember to maintain the airway patency, resolve the phlegm, wet the trachea, aspirate sputum with flexible bronchofiberscope, maintain the drainage fluently, and promote pulmonary rehabilitation. If there is a small leakage, it is suggested to use negative pressure suction earlier with continuous 5–10 cmH$_2$O negative pressure. What more, it is also very important to correct the pulmonary contusion caused by trauma, limit the amount of liquid, and reduce pulmonary edema. If there is bronchial rupture, it is necessary to avoid using positive pressure ventilation although this is one of the effective methods for the treatment of pulmonary edema (35). Early use of hormones can be helpful to the edema of stoma and pulmonar, but there are also some scholars believed that this might increase the risk of infection (36).

Conclusions

Early diagnosis is a prerequisite for the successful treatment of bronchial rupture patients, in which successful intubation is a basic guarantee. Reasonable treatment of complications can reduce the mortality rate, at the same time well intraoperative airway management makes the stomas more precise. For these patients as soon as diagnosis is made we should take active surgical treatment. The key to successful operation lies in low tension neat anastomosis. All of above can ensure the successful rehabilitation and a good quality of life after surgery.

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Footnote

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Characteristics of endobronchial tuberculosis patients with negative sputum acid-fast bacillus

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Objective: Endobronchial tuberculosis (EBTB) is defined as a tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence, with or without parenchymal involvement. In this study, clinical, radiological and bronchoscopic characteristics of cases diagnosed to have EBTB were evaluated.
Methods: Sixteen patients with at least three negative sputum examinations for acid-fast bacillus (AFB) and diagnosed as having EBTB on the histopathological examination of bronchoscopically obtained specimens showing granulomatous structures with caseation necrosis and/or positive AFB-culture on the microbiological examination of bronchoscopically obtained specimens were included in our study. Age, sex, symptoms, tuberculin skin test (TST), microbiological examination results and radiological findings were recorded. Bronchoscopical lesions were classified according to Chung classification.
Results: EBTB was found to be more common in females. Most common symptoms were cough (100%), sputum (75%), weight loss (62.5%), hemoptisis (37.5%), chest pain (25%) and dyspnea (12.5%). Radiological examination findings revealed consolidations/infiltrations (87.5%), nodular lesions (37.5%), cavitary lesions (25%), unilateral (43.7%) or bilateral hilar widening (31.2%) and atelectasia (25%). Middle lob syndrome was seen in three cases. Most common lesions observed bronchoscopically were active caseous lesions, granular lesions, edematous hyperemic lesions, tumorous lesions, fibrostenotic lesions respectively. In all cases "granulomatous inflammation showing caseation" was shown in the histopathological examination of biopsy specimens.
Conclusions: EBTB can cause various radiological and bronchoscopical findings. In most of the cases distinct response is seen to antituberculous treatment. Bronchial stenosis is an important complication. Treatment should be given as soon as possible to avoid it.

Keywords: Endobronchial tuberculosis (EBTB); bronchoscopy; radiology; histopathology; microbiology

Introduction

Endobronchial tuberculosis (EBTB) is defined as a tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence, with or without parenchymal involvement (1,2). EBTB was first shown in 1698 by Richard Morton in an autopsy case died due to tuberculosis (3). The pathogenesis of EBTB is not well understood. Nevertheless five potential mechanisms was believed to be responsible from the development of endobronchial infections caused by M. tuberculosis: (I) direct invasion from an adjacent paranchymal focus; (II) implantation of the organisms from infected sputum; (III) haematogenous spread; (IV) erosion of a lymph node inside a bronchus; (V) lymphatic drainage from the parenchyma towards the peribronchial region (4-7). Since bronchoscopy is not routinely performed to all patients with pulmonary tuberculosis, actual incidence of EBTB could not be evaluated. For this reason, the proportion of endobronchial involvement

in active pulmonary tuberculosis is variable according to the literature. In a study it is reported that 5.88% of pulmonary tuberculosis cases were shown to have EBTB (4); in another study this ratio was reported to be 10-40% (7) and in other two studies this ratio was shown to be 50% (8,9). EBTB may mimic diseases like bronchial asthma, pneumonia and lung cancer (10,11). EBTB may affect any region of the tracheobronchial tree. If it affects the middle lob, it causes collapse, since the entry of the middle lob is narrow. This is known as middle lob syndrome (12,13). Chung classified forms of EBTB into seven subtypes by bronchoscopic finding: actively caseating, edematous-hyperemic, fibrostenotic, tumorous, granular, ulcerative, and nonspecific bronchitic (14). EBTB is a severe situation with high bacilli lode, and may cause complications with high morbidity like bronchial stenosis; early diagnosis and treatment is therefore mandatory (1,4,9). The course and prognosis of endobronchial TB are variable, ranging from complete clearance to severe bronchostenosis (15). In this study, clinical, radiological and bronchoscopic characteristics of cases diagnosed to have EBTB were evaluated.

Patients and methods

One hundred seventy eight patients with active lung tuberculosis (128 AFB positive, 50 ARB negative) attending to Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital between 2008 and 2012 were examined. Twenty of 50 AFB (-) patients were given anti-tuberculous therapy as clinical and radiological. Thirty of 50 AFB (-) patients were performed fiberoptic bronchoscopy (FOB) and determined endobronchial lesion in 16 patients. Fourteen patients with normal FOB were similar to 16 patients with endobronchial lesion as characteristic of clinical and radiological. These 16 EBTB patients with at least three negative sputum examinations for AFB and diagnosed as having EBTB on the histopathological examination of bronchoscopically obtained specimens showing granulomatous structures with caseation necrosis and/or positive AFB-culture on the microbiological examination of bronchoscopically obtained specimens were included in the study. Our study was a retrospective observational study. This study was performed according to the Helsinki declaration 2008 and written informed consents were obtained from all patients. Age, sex, symptoms, tuberculin skin test (TST) results, microbiological examination results and radiological

findings on postero-anterior chest X-rays of the cases were recorded. Computerized tomography (CT) findings of the cases were revised. Bronchoscopical lesions were classified according to Chung classification (14). Actively caseating lesions were grouped as type 1, oedematous hyperemic lesions as type 2, fibrostenotic lesions as type 3, tumorous lesions as type 4, granular lesions as type 5, ulcerative lesions as type 6 and non-specific bronchitic lesions as type 7. After diagnosis, cases were treated under direct observation with 5 mg/kg·day izoniacid, 10 mg/kg·day rifampicin, 20 mg/kg·day ethambutol and 25 mg/kg·day pyrazinamid. Response to treatment were checked with chest X-ray and thorax CT examinations. After a two month therapy patients becoming AFB culture negative and not showing any resistance to antituberculous therapy were continued to be treated with two drug combination. Antituberculous treatment was stopped after a 6-month treatment. Bronchoscopy was repeated in patients with delayed recovery and treatment was continued for nine months. Systemic corticosteroid treatment was added to patients with bronchial stenosis.

Results

Age, sex, comorbidity factors, symptoms and TST were given in *Table 1*. EBTB was found to be more common in females (M/F ratio: 4/12=1/3), prior bronchoscopy cases were at least three times examined for sputum AFB (with Ziehl-Neelsen stain) and all were AFB negative. In 4 of the cases bronchoscopic lavage AFB were positive, in other 10 cases AFB cultures were positive (*Table 2*). Most common symptoms were cough (16 cases, 100%), sputum (12 cases, 75%), weight loss (10 cases, 62.5%), hemoptisis (6 cases, 37.5%), chest pain (4 cases, 25%) and dyspnea (2 cases, 12.5%) respectively. Radiological examination findings revealed consolidations/infiltrations (14 cases, 87.5%), nodular lesions (6 cases, 37.5%), cavitary lesions (4 cases, 25%) and unilateral (7 cases, 43.7%) or bilateral hilar widening (5 cases, 31.2%) and atelectasia (4 cases, 25%). Middle lob syndrome because of collapse was seen in 3 cases (*Figures 1,2*). Most common lesions observed bronchoscopically were active caseous lesions (Type 1, in 6 cases, 37.5%). Granular lesions (Type 5) were seen in 3 cases (18.7%), tumorous lesions (Type 4) in 2 cases (12.5%), edematous hyperemic lesions (Type 2) in 2 cases (12.5%), edematous hyperemic (Type 2) + fibrostenotic (Type 3) lesions were seen in 1 case (6.2%), granular (Type 5) + fibrostenotic (Type 3) lesions (6.2%) were seen in

Table 1 Characteristics of the patients.

	Age	Sex	Comorbidity factors	The most obvious symptom	TST
1	63	F	RA	Dyspnea	+
2	33	F	–	Cough	+
3	44	M	COPD	Cough	+
4	34	F	–	Cough	+
5	29	F	–	Hemoptysis	+
6	18	F	A	Cough	+
7	59	F	DM (type 2)	Weight loss	+
8	32	F	–	Cough	+
9	72	F	PU	Hemoptysis	–
10	25	M	–	Weight loss	+
11	67	F	DM (type 2)	Cough	–
12	39	M	–	Cough	+
13	22	F	–	Cough	–
14	24	F	–	Cough	+
15	31	M	–	Cough	+
16	27	F	DM (type 1)	Cough	+

Abbreviations: F, female; M, male; TST, tuberculin skin test; RA, rheumatoid arthritis; COPD, chronic obstructive pulmonary disease; A, asthma; DM, diabetes mellitus; PU, peptic ulcer.

1 case (*Table 2*, *Figures 1-4*). In all cases "granulomatous inflammation showing caseation" was shown in the histopathological examination of biopsy specimens. Lesions were totally recovered in 14 patients treated with standard anti-tuberculous treatment. Only two patients with middle lob syndrome (edematous – hyperemic + fibrostenotic and granular + fibrostenotic) needed treatment longer than six months for complete recovery, they were treated for nine months and systemic corticosteroids were added because of stenotic appearance; partial response were observed.

Discussion

EBTB contains rather high amounts of tuberculosis bacilli. Early diagnosis and treatment is important for prevention of the spread of tuberculosis and complications like cicatricial bronchostenosis due to endobronchial involvement (16). More than half of the EBTB cases were reported to be younger than 35 years. Different female/male ratios were reported. It was shown that it is more common in young woman than male sex (4,15,17). It was

more common in young woman also in our study with a male/female ratio (M/F: 1/3). However in a recent study it was also common in elderly (8); sites of tracheabronchial invasion were reported to be different in young and elderly patients (18). In elderly patients lobar and segmental bronchial invasion was more common, whereas in younger patients involvement of trachea and main bronchi were seen generally and middle lobe syndrome was more common in elderly (19). In our study all of the three cases of middle lobe syndrome were females and their ages were 29, 63 and 67.

Classical symptoms of EBTB are cough, difficultly expectorated high viscose sputum, wheezing, fever, chest pain and haemoptysis (16). These symptoms may be seen in other respiratory diseases, so they do not help for the early diagnosis of EBTB. The most common symptom is persistent cough, which is thought to be related to the endobronchial inflammation (16). In a study the most common symptoms reported were cough, sputum, dyspnea and fever (20). In our study most common symptoms were cough and difficult sputum expectoration followed

Table 2 Microbiological, bronchoscopic and histopathological features in the patients.

| Case | Microbiology | | Bronchoscopic localization | Bronchoscopic classification | Histopathology CGI |
| | Sputum | Lavage | | | |
	AFB/culture	AFB/culture			
1	–/+	–/+	RML	Type 2 + Type 3	CGI
2	–/–	–/–	RUL	Type 6	CGI
3	–/–	–/+	LUL + LLL	Type 1	CGI
4	–/–	–/–	RLL	Type 5	CGI
5	–/+	+/+	RML	Type 3 + Type 5	CGI
6	–/–	–/–	RUL	Type 1	CGI
7	–/–	–/–	LLL	Type 5	CGI
8	–/+	+/+	RUL	Type 1	CGI
9	–/–	–/+	LLL	Type 4	CGI
10	–/–	–/+	LUL	Type 1	CGI
11	–/+	+/+	RML	Type 4	CGI
12	–/–	–/–	RUL + RML	Type 1	CGI
13	–/–	–/+	RUL	Type 2	CGI
14	–/+	+/+	LUL	Type 2	CGI
15	–/–	–/–	RLL	Type 5	CGI
16	–/–	–/+	LUL	Type 1	CGI

AFB, acid fast bacil; CGI, caseating granulomatous inflammation; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; Type 1, actively caseating; Type 2, edematous-hyperemic; Type 3, fibrostenotic; Type 4, tumorous; Type 5, granular; Type 6, ulcerative.
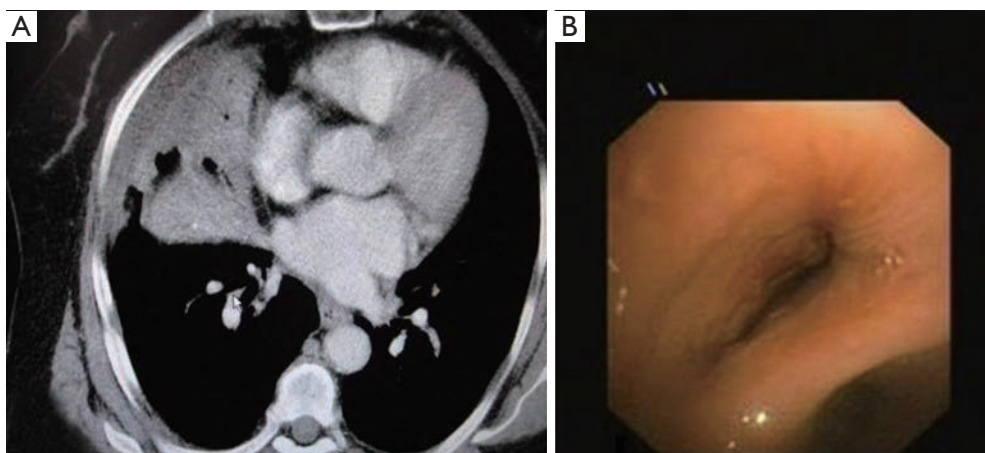

Figure 1 (A) Thorax CT showing right middle lobe atelectasia (middle lobe syndrome); (B) Bronchoscopy of a case with narrowing of right middle lobe entrance almost totally due to edema and stenosis.
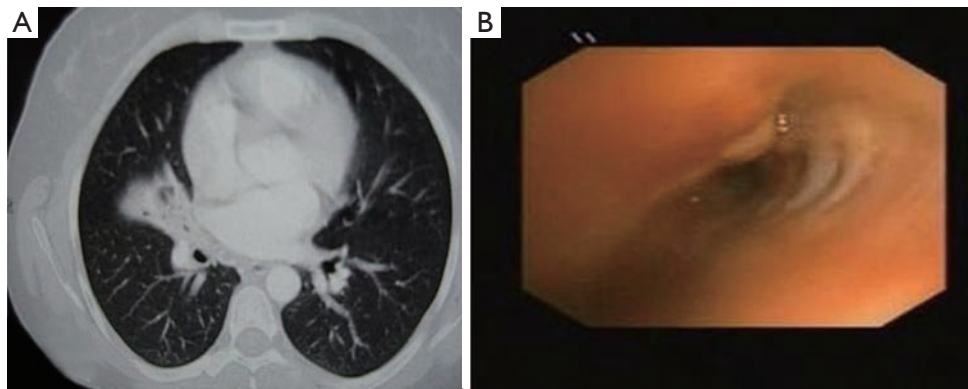
Figure 2 (A) Thorax CT showing right middle lobe partial atelectasia; (B) Bronchoscopy revealing granular lesion in the medial wall of the right middle lobe entrance and partial fibrostenosis.
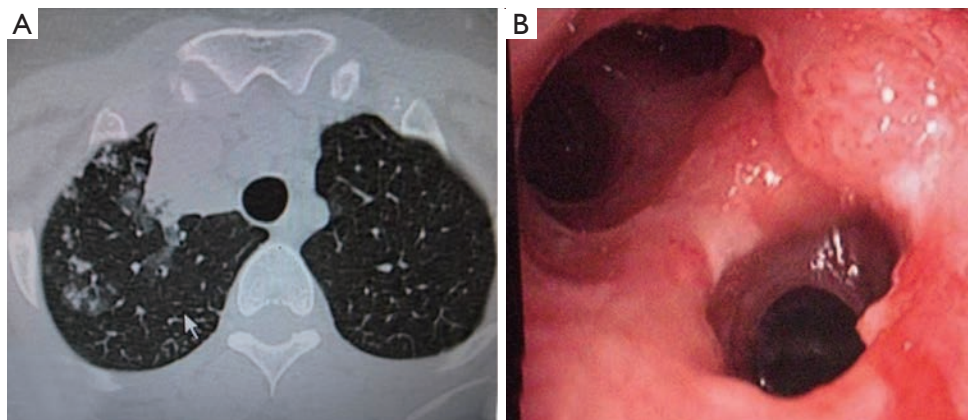

Figure 3 (A) A perimediastinal—perivascular triangle shaped consolidation of the right upper lobe anterior region with scattered paranchymal asino-nodular infiltrations around it, shown with thorax CT; (B) Right upper lobe with only two segments anatomically, instead of normal three segments. Polipoid—tumorous, whitish caseous and ulcerous lesions on the entrance of the segment compatible with the posterior segment.

by weight loss, haemoptysis, chest pain and dyspnea in frequency.

Microbiological examination of sputum is the first coming main examination leading to diagnosis in EBTB. Nevertheless unlike paranchymal diseases AFB positivity in EBTB is between 16% to 53.3% in most favorable conditions. In a study performed by Lee et al. sputum ARB positivity prior bronchoscopy was found to be as low as 17% (21). This ratio increased to 73.6 % with culture (7). Sputum AFB was negative in all of our cases at the beginning of the study. In our study, bronchoscopic lavage revealed positive AFB in 4 cases and positive culture in 10 cases.

Radiological findings of EBTB may vary, different findings like patchy alveolar infiltrations, atelectasia, hilar widening, pleural effusion, mass and cavitary lesions may be seen (16). EBTB can not be excluded in the case with normal chest X-ray, because 10% to 20% of cases may have normal chest X-ray (16). In the study conducted by Lee et al. it was reported that common radiological findings of EBTB were consolidations and volume loss, and these findings were seen in 83.4% of the cases (21). Chest X-ray frequently showed atelectasis. This would make it difficult to differentiate EBTB not only from bronchial asthma, but also from bronchogenic carcinoma in old age (21). Thorax CT is a helpful tool to show endobronchial masses, widened mediastinal-hilar lymph nodes, helps with better identification of paranchymal lesions and evaluation of
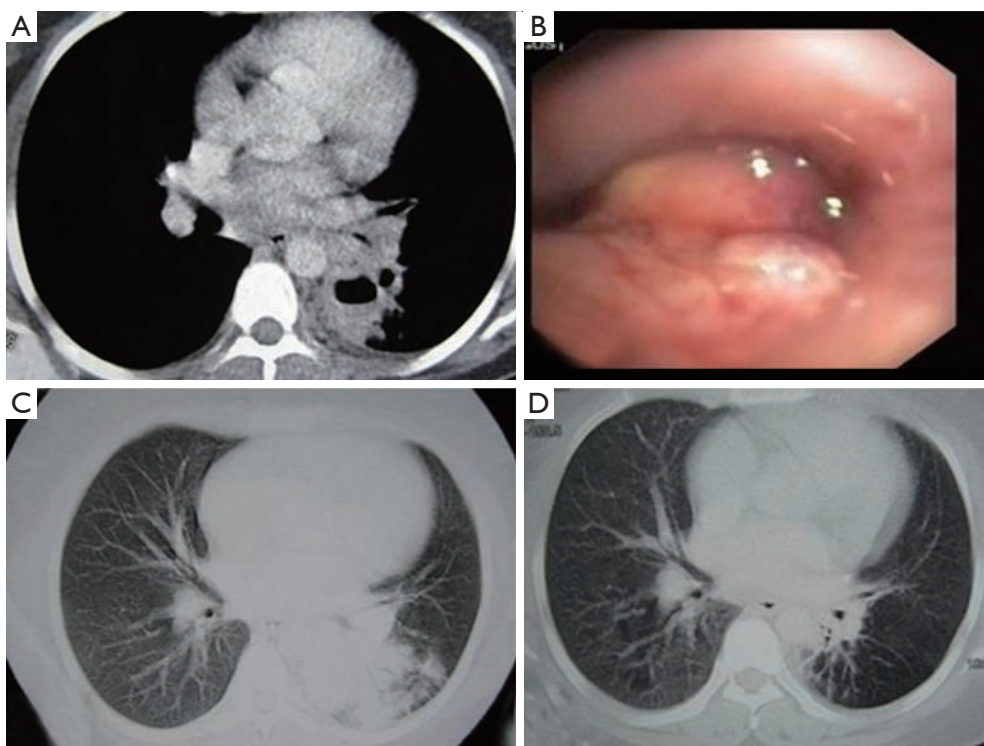
Figure 4 (A) Mediastinal window image on the thorax CT, partial volume loss of the left lower lobe, irregularly bordered lesion; (B) Tumoral lesion visualized with bronchoscopy, lobulated appearance of the lesion obstructing the entrance of the left lower lobe of basal segment; (C) Paranchymal window image on the thorax CT of the same patient, irregularly bordered consolidated lesion, partial volume loss of the left lower lobe; (D) Improvement of the lesions after standard anti-tuberculous treatment.

cases like stenosis or obstruction (2,16). In a study multiple lobar lesions, exudative shadows and atelectasis were the most common radiological findings (20). Radiological findings of our cases listed according to their frequency were consolidations/infiltrations, nodular lesions, cavitary lesions and uni- or bilateral hilar widening.

Bronchoscopy should be performed in suspicious cases like unexplained cough, wheezing, dyspnea or haemoptysis (22). Persistent segmental or lober collaps, lobar infiltrations and obstructive pneumonia findings on chest X-ray examination are also indications for bronchoscopy (7). In a study common right upper lobe and right main bronchial EBTB were diagnosed with bronchoscopy (21). In our study, common bronchoscopic localization were right upper lobe (RUL), left upper lober (LUL) and right middle lobe (RML).

In a study active caseous type was reported to be most common (17). In recent studies it was reported that most common bronchoscopic finding was edematous-hyperemic type (8,23). This is the most common type of bronchoscopic finding in middle lobe syndrome (19). Sputum or bronchial lavage AFB is generally positive in active caseous type, but edematous type is hard to diagnose, and sputum and bronchial lavage AFB is generally negative; therefore tuberculosis culture and histopathological examinations should be performed (19). It is also reported that while active caseous type recovers almost completely, edematous or active caseous + edematous type changes to fibrostenotic type in more than 60% of cases (4). Four of the subtypes—actively caseating, edematous-hyperemic, fibrostenotic, and tumorous EBTB—show varying degrees of luminal narrowing of the bronchus, while the other three subtypes—granular, ulcerative, and nonspecific bronchitic EBTB—do not (4). Similarly, it is reported in a study that early stage exudative, granular and ulcerative lesions recovered without sequel; caseous and tumorous lesions of advanced disease might lead complications such as bronchostenosis causing bronchectasia (16). A study conducted by Um SW et al. revealed that factors related to development of bronchial

stenosis were age over 45 years, pure or combined fibrostenotic subtype and symptoms lasting more than 90 days prior treatment (15). In our study most common lesions observed bronchoscopically were active caseous lesions. These were followed by granular, edematous-hyperemic, tumorous, fibrostenotic and ulcerative lesions with decreasing frequencies. Treatment responses of our cases were followed by control thorax CTs. There are literature reporting that follow up with CT might be an alternative to follow up with bronchoscopy (16). There are also some reports proposing that findings related to a development of bronchial stenosis could also be shown with CT examination (24). In our study, two middle lobe cases without a complete recovery after treatment, undergone control bronchoscopy in addition to control CT examinations and the findings were concordant with control CTs. As reported in other studies mentioned above pure or combined fibrostenotic types were found to be responding slower to treatment as seen in the two cases in our study.

Corticosteroids have been used empirically in the treatment of tuberculosis in an attempt to prevent fibrosis. However, the value of using corticosteroids for EBTB is uncertain (25). Though literature reporting that steroid addition did not help with improvement or clinical healing (5,6,26) there are literature arguing that oral or inhalated steroids effect improvement and clinical healing positively in some types of EBTB (2,27,28). Corticosteroids are likely to be beneficial in earlier stages when hypersensitivity is the predominant mechanism, but are unlikely to be helpful in more advanced cases when extensive fibrosis is present. Close follow-up is advisable as stenosis may develop later despite antituberculosis chemotherapy with or without corticosteroids (21). Except the two cases all of our cases were healed totally with standard antituberculous treatment (quaternary treatment for the first two months, binary treatment for the following four months, totally six months treatment). There were delayed response to treatment due to bronchostenosis in two of our cases (a case of edematous hyperemic + fibrostenotic type and a case with granular + fibrostenotic lesions). In these cases antituberculous treatment were continued for nine months and oral corticosteroids were added, however partial response to stenosis were obtained. This may support the findings reported in some literature mentioned above that corticosteroids do not help much with improvement in the treatment of bronchial stenosis.

Conclusions

EBTB can cause various radiological and bronchoscopical findings. In most of the cases distinct response is seen to antituberculous treatment. Bronchial stenosis is an important complication and should not be disregarded. Patients with old age, having symptoms lasting for a long time prior treatment and having fibrostenotic type of disease are at higher risk. Treatment should be given as soon as possible to avoid this complication.

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None.

Footnote

Conflicts of Interest: The authors declare no conflict of interest.

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Endobronchial tuberculosis—a review

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Abstract: Endobronchial tuberculosis (EBTB) is a tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence. Patients may present with symptoms secondary to disease itself or from the complication of disease like endobronchial obstruction. Diagnosis requires a high index of suspicion. Computed tomography (CT) and bronchoscopy along with microbiological investigations are the most useful diagnostic tools for the confirmation as well as for the evaluation of the tracheobronchial stenosis. The goals of treatment are eradication of tubercle bacilli with anti-tubercular medications and the prevention of airway stenosis. Interventional Bronchoscopic techniques and surgery is required for those patients who develop severe tracheobronchial stenosis that causing significant symptoms including dyspnea, repeated post obstructive pneumonia or bronchiectasis.

Keywords: Endobronchial tuberculosis (EBTB); bronchoscopy; complications; radiology; endobronchial obstruction

Introduction

Tuberculosis (TB) is a major global health problem. It affects millions of people each year and ranks alongside the human immunodeficiency virus (HIV) as a leading cause of death worldwide. In 2014, there were an estimated 9.6 million new TB cases and 1.5 million deaths worldwide according to WHO (1). Endobronchial tuberculosis (EBTB) or tracheobronchial TB is a special form of TB and is defined as tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence (2). Involvement of trachea and bronchi by TB was first described by Richard Morton, an English physician in 1698 (3). This form of TB is difficult to diagnose because the lesion is not evident in the chest radiograph frequently and thus delaying treatment. Further investigations like computed tomography (CT) scan of chest and bronchoscopy are often needed to diagnose and evaluate bronchial lesions such as stenosis or obstruction. The evolution and prognosis of EBTB is variable, going from complete resolution to residual severe tracheobronchial stenosis (4). The most important goal of treatment in active EBTB is eradication of tubercle bacilli. The second most important goal is prevention of bronchial stenosis. Because of its increasing incidence, significant morbidity and potential mortality, early diagnosis and treatment is necessary to prevent complications. This article has reviewed the latest updates about the pathogenesis, signs, symptoms, diagnostic tools, treatment and prognosis of this disease entity.

Epidemiology

Exact incidence of EBTB is not known as bronchoscopy was not routinely performed in all cases of pulmonary TB. Prior to era of antituberculous therapy, endobronchial TB was relatively more common (5,6). In 1943 a study done in a TB sanatorium, EBTB were observed in 15% of cases via rigid bronchoscopy and in 40% of cases at autopsy (5). Since

the availability of antituberculous therapy, the reported incidence of EBTB in pulmonary TB patients varies greatly, ranging from 6% to 54% in various studies (7-11).

EBTB has been proposed to be more common in females (7,11,12). Exact phenomenon is not well known but the possible causes include a longer exposure to tubercle bacilli, as female patients have less expectorated sputum containing bacilli due to sociocultural and aesthetic factors. Second also a structural difference may play a role as female bronchi are narrower than those of males, which may make females more susceptible to EBTB (11-14).

Majority of patients with EBTB usually presents in second or third decade (12,13). The second peak is also described in old age (13,15). The possible mechanism is likely due to diminished immune response and complicating comorbid illnesses resulting in reactivation or reinfection by exogenous MTB and increasing bronchoscopies in elderly patients (11).

Pathology and pathogenesis

EBTB may affect any part of the bronchial tree. Primary bronchi, bilateral superior lobar bronchi and right middle lobar bronchus are the commonly affected sites. Jung *et al.* classified EBTB by the number of involved levels (11). Single-level EBTB was defined when only one site of trachea, main bronchus or lobar bronchus was involved. EBTB that involved two or more bronchial levels was defined as multiple-level EBTB, while that occurred proximal to the lobar bronchi was defined as central EBTB which had a potential to develop symptomatic stenosis (11).

Pathologically EBTB may affect any layer of the tracheobronchial wall including lamina muscularis and cartilage (16). Pathological changes mainly include mucosal and submucosal tuberculous infiltration, ulcer, granuloma, fibroplasias and tracheobronchial stenosis. Initially mucosal and submucosal hyperemia is present secondary to infiltration of inflammatory cells, mainly lymphocytes. Later tubercular nodules are formed in the diseased region followed by caseous necrosis in the nodules and mucosal ulceration (7,17). This ulcer may progress into the tracheobronchial wall and become deep-part ulcer, or may become inflammatory hyperplastic polyps protruding the tracheobronchial lumen like tumor. In advanced stages, fibrous hyperplasia and contracture develop and cause tracheobronchial stenosis (7,17,18), whose incidence may reach up to 68% in the initial 4–6 months and rises further with elongating course of the disease (12).

The exact pathogenesis of EBTB is not yet fully understood, the five proposed mechanisms of infection described in literature include (I) direct extension from an adjacent parenchymal focus; (II) implantation of organisms from the infected sputum; (III) haematogenous dissemination; (IV) lymph node erosion into a bronchus; and (V) spread of infection via the lymphatics (7,13,19).

The development and progression of EBTB is a complex phenomenon and various cytokines may also play an important role in pathogenesis in addition to local factors. Elevated levels of interferon gamma and TGF-beta in bronchial lavage fluids may be related to pathogenesis and progression of EBTB (13,20). Changes in the levels of TGF-beta observed in the serum after treatment have been implicated in the development of bronchial stenosis during the course of the disease (20).

Clinical features

The clinical manifestations of EBTB vary widely according to the site, extent of involvement, or stage of the disease, and may be acute or insidious in onset. Symptoms may be secondary to disease itself or from the complication of disease like endobronchial obstruction.

Systemic symptoms of TB like anorexia, generalized weakness and weight loss are usually reported in more than 50% of the patients (12,21). Cough is the most common symptom and present in 70–80% of the patient (12,21,22). Cough could be dry or with bronchorrea especially when EBTB is a part of cavitory TB (23). Fever is usually low grade but may become marked with advanced cavitory disease (12,22). Hemoptysis may occur in 15–40% of the patient but is usually mild but sometime massive hemoptysis may occur (22). Chest pain of variable intensity may be present in 15–25% of patients (9,24). Localized wheezing and decreased breath sounds if there is a stenosing effect by the endobronchial lesion (25,26). However, these symptoms and signs are nondistinctive as EBTB can simulate other diseases like malignancy (27), bronchial asthma (28), foreign bodies, and recurrent pneumonia (12,15,25).

Diagnosis

Early diagnosis leads to appropriate management that favorably changes the course of EBTB. The diagnosis of EBTB is more difficult as compared to pulmonary TB because of variable and nondistinctive clinical manifestations. Although sputum examination is the essential and first step towards the diagnosis of EBTB, bronchoscopy and CT are the methods of choice for

accurate diagnosis of bronchial involvement and its complications (7,11,12).

Sputum examination

Bacteriological examination of sputum smear like acid-fast bacilli (AFB) staining is the most important and commonly used test to diagnose EBTB; however the diagnostic yield is low. Freshly expectorated sputum should be taken for acid-fast bacilli staining in order to increase diagnostic success (13). Positivity of sputum AFB smear in EBTB is variable in different studies ranging from 16% and 53% but a negative sputum smear does not exclude the diagnosis of EBTB (8,13,29). One of the possible reasons suggested for this low yield is mucus entrapment by proximal bronchial granulation tissue. EBTB with ulceration and mucosal involvement has a higher yield of sputum smear and culture positivity (8,12,13).

Newer nuclear amplification tests like Xpert MTB/RIF assay and line probe assay (Geno Type MTBDR Plus) shows better results than sputum AFB smear and are recommended in suspected cases but still very limited data is available in utility of these tests in EBTB (30).

Bronchoscopy

Bronchoscopy is the most valuable method to establishing early diagnosis and assessing prognosis in EBTB. Bronchoscopic procedures such as biopsy, brushings, needle aspiration, bronchoalveolar lavage (BAL) and endobronchial ultrasonography can be used to establish diagnosis (8,11,30,31). Bronchoscopy is also important to exclude any other underlying or concomitant disease like malignancy.

The bronchoscopic appearance of EBTB is closely related to the pathological changes and has been classified into seven subtypes by Chung *et al.* (7) but none is exclusive enough to establish the diagnosis by appearance alone: (I) nonspecific bronchitic (tracheobronchial mucosa only is mildly swollen and/or hyperemia); (II) edematous-hyperemic (tracheobronchial mucosa is severely swollen and hyperemic); (III) actively caseating (tracheobronchial mucosa is swollen, hyperemic and covered with a large amount of whitish cheese-like material); (IV) granular (tracheobronchial mucosa appears severely inflammatory and is scattered by rice-like nodules); (V) ulcerative (tracheobronchial mucosa ulcerate); (VI) tumorous (hyperplastic focal tissue shapes, intraluminal mass like tumor); and (VII) fibrostenotic (tracheobronchial lumen narrows due to fibrous hyperplasia and contracture). Each subtype of EBTB has its own characteristic appearance

and has been proposed to be closely related to the extent of disease progression. The prominent lymph nodes are seen during bronchoscopy as grayish-yellow masses through the bronchial mucosa; while hemorrhage, granulation tissue fistula formation and caseous material draining into bronchus may also be seen.

Bronchoscopic biopsy is the most validated method for confirming the diagnosis. The yield of bronchial biopsies to diagnose EBTB is 30% to 84% of patients in various studies (13,32).

The AFB smears and culture yield in BAL is high then the sputum examination. A study done by Ozkaya *et al.* showed that microbiologic and smear examination of BAL fluid was positive for AFB in 26% of the patients with the highest rates found in granular-type cases (75%) while the cultures of BAL fluids for Mycobacterium TB were positive in 39.1% of patients, and the positivity was highest in granular-type cases (75%) in histologically proven sputum smear negative cases (8).

Chest radiograph

Chest radiograph may be normal in about 10–20% of patients with EBTB (7,25). Any chest radiographic findings are not specific for the diagnosis of EPTB. The most common abnormality on chest X-ray is the patchy parenchymal infiltrates in the affected lobe. The other chest X-ray findings are depending on the severity of bronchostenosis and may present as persistent segmental or lobar collapse, lobar hyperinflation, obstructive pneumonia and mucoid impaction. (25,33). Erosion of calcified hilar nodes into adjacent bronchi, known as broncholithiasis, may also result in segmental collapse or over inflation. Other radiological findings include fibrotic and calcific focus, cavity, bronchiectasis, intrathoracic lymphadenitis and pleural effusion. Different radiological signs are often seen in the same patient (7,25,34).

CT scan

In recent years, because of high resolution power and minimal partial volume effect, high resolution computed tomography (HRCT) has been found to be superior to conventional chest radiography and standard CT in the localization of disease in the pulmonary lobule and in the evaluation of pulmonary parenchymal disease. Endobronchial involvement in pulmonary TB has been reported as high as 95% and 97% with HRCT scanning in various studies (35,36). Early findings include centrilobular

nodules or linear structures which are well defined lesions 1–4 mm thick, separated by more than 2 mm from the pleural surface or interlobular septa. Later multiple branching linear structures of similar caliber originating from a single "stalk" (the "tree-in-bud" appearance) were commonly seen in patients with extensive bronchogenic spread (36). Other CT findings include segmental bronchial narrowing with concentric wall thickening, complete endobronchial obstruction, extrinsic obstruction by adjacent adenopathy and scarring (13,32,36). Even with a highly suspected CT chest, bronchoscopy with a histopathological or microbiological confirmation is still required for a definite diagnosis of EBTB (7).

Complications

The most common complications of EBTB are bronchial stenosis and stricture formation that may develop in more than two third of patients despite of adequate medical management. Patients can also develop severe airway obstruction and respiratory failure if the larger airways are involved. Another common complication is post obstructive bronchiectasis that leads to frequent pneumonia and hemoptysis (13,29). A group of patient also developed persistent obstructive airway disease as a sequel of EBTB.

Treatment

The main goals of EBTB treatment are eradication of MTB infection and prevent tracheobronchial stenosis. The course and prognosis is mainly related to the degree, the extent and the duration of lesions before treatment. So, early diagnosis and adequate treatment is necessary to prevent complications.

The treatment of EBTB is similar to pulmonary TB. Five standard first line drugs are used for the treatment of EBTB which includes Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z) and Streptomycin (S).

Local antituberculosis medications have also been used in the treatment of EBTB with variable results. These include the inhalation of nebulized antituberculosis drugs, the diseased region lavage with antituberculosis drugs and the submucous injection of antituberculosis drugs. The common locally used anti-tuberculosis drugs include isoniazid or streptomycin (16).

Corticosteroids have been used as an adjunct therapy in treatment of EBTB but their role is still controversial. Corticosteroids may be useful in the earlier stages of EBTB when hypersensitivity is the predominant mechanism but in later stages they have less likely to be helpful rather

may cause detrimental effects. Corticosteroids have shown improvement in clinical outcomes when used in children (13,37). The beneficial role in children might be contributed by anti-inflammatory response thereby preventing bronchial compression resulting from erosion of lymph nodes into bronchial lumen however this has not been shown to prevent bronchostenosis in adults (25,38).

Corticosteroids have also been tried locally. Rikimaru showed that the healing time of ulcerous lesions was shorter and bronchial stenosis was less severe, in patients treated with aerosol therapy, consisting of streptomycin 100 mg, dexamethasone 0.5 mg and naphazoline 0.1 mg administered twice-daily along with conventional oral therapy (39). In another study submucosal methylprednisolone injection also demonstrated resolution of EBTB (25,40). The role of corticosteroids needs to be further evaluated in larger prospective trials before its regular use in adult patients.

The development of bronchial stenosis or strictures is the most common sequel and usually irreversible despite adequate antituberculous therapy and therefore requires airway patency to be restored either with bronchoscopic or surgical interventions (41). There are various bronchoscopic interventions to relieve airway stenosis including balloon dilatation, stent insertion, laser and cryosurgery (42). Fibrostenosis is the indication of balloon dilatation which can be achieved via a rigid or flexible bronchoscope. Bronchial wall rupture is one of the complications of balloon dilatation and should avoid excessive inflation (42). Persistent airway stenosis following balloon dilatation has been described especially if active inflammation, calcification and malacia are evident. The incidence of restenosis is about 37.5% a month after balloon dilatation (43).

Patients who require more than one session of balloon dilatation need stenting or ablative procedures (44). Both metal and removable silicon have been used but the removable stents are preferable to avoid long term stent-related complications. Both types of stent have complications like migration, stent fractures, retained secretions, colonization of stent material, and development of granulation tissue and need regular followups (44).

In the setting of alleviating central airway obstruction, laser resection, electro cautery, and argon plasma coagulation can provide immediate relief (45). Laser resection is the application of laser energy delivered via rigid and/or flexible bronchoscopes in order to manage different endobronchial lesions. The neodymium: yttrium aluminum garnet (Nd-YAG) equipment is the most widely used for bronchoscopic Interventions. The main indication for laser

bronchoscopy comprises obstructive lesions of the trachea, main bronchi and the lobar orifices that compromise ventilation and produce severe symptoms including dyspnea, stridor, intractable cough, and hemoptysis (13,45).

Cryosurgery is another option and it is safer than balloon dilatation or laser. There is a less chances of bronchial wall perforation is with cryosurgery as compared to other procedures but it requires repeated procedure and time consuming (13,46).

Severe tracheobronchial stenosis, which causes severe bronchiectasis, lung collapse, repeated pulmonary infection or frequent hemoptysis may require thoracic surgery like pneumonectomy or lobectomy (47). Newer surgical techniques are also emerging to restore air way patency in endobronchial stenosis.

Conclusions

EBTB is a special form of TB which is associated with significant morbidity and potential mortality. Early diagnosis and aggressive treatment with antituberculous chemotherapy is necessary in the management of EBTB to prevent complications like tracheobronchial stenosis. The role of corticosteroids is still controversial but can be used in selected patients. For early and accurate diagnosis, bronchoscopy should be performed initially in suspected cases. If medical treatment is not sufficient in the management, then various bronchoscopic and surgical techniques should be utilized to preserve lung function. Future research is required to know the exact pathogenesis and the course of disease. Additionally, efforts should be undertaken to control the transmission of this disease entity by infection control measures.

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Footnote

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Tracheobronchial tuberculosis

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Abstract: Tracheobronchial tuberculosis (TBTB) is reported in approximately 10% to 39% of the patients with pulmonary tuberculosis. It is defined as the tubercle infection of the trachea and or bronchi. Due to its non-specific presentation, insidious onset and normal chest radiography in about 10–20% of the patients, the diagnosis is delayed. Bronchoscopy is the most definite method of diagnosis which provides adequate specimens for microbiological and histopathological diagnosis. Tracheobronchial stenosis is one of the most common long term complications of TBTB resulting in significant morbidity. It is estimated that 90% of patients with TBTB have some degree of tracheal and or bronchial stenosis. In this review article, we will discuss the pathogenesis, symptoms, imaging, bronchoscopic findings, and treatment of TBTB and management of tracheobronchial stenosis.

Keywords: Tuberculosis induced stenosis; endobronchial stenosis; tracheobronchial stenosis; endobronchial tuberculosis; bronchial stenosis; tracheobronchial tuberculosis (TBTB)

Introduction

The prevalence of tuberculosis-induced tracheobronchial stenosis varies as a function of the prevalence of tuberculosis, and is estimated to be as high as 10% to 40% in patients with pulmonary tuberculosis.

Tracheobronchial tuberculosis (TBTB) is diagnosed on histopathological examination of bronchoscopically obtained specimens showing granulomatous inflammation with caseation necrosis and/or positive acid fast bacilli culture on the microbiological exam. Specimen for culture can also be obtained from sputum but it is less sensitive compared to bronchial washing, biopsy or bronchoalveolar lavage; as described by Qingliang *et al.* in China where only 3/22 (13%) patients were sputum acid fast bacilli positive, and the remainder required bronchoscopic sampling for the diagnosis (1,2). The diagnosis of TBTB is often delayed due to its non-specific clinical symptoms. The course of endobronchial tuberculosis is highly variable and can range from complete resolution of the disease to fibrotic central airway obstruction (3).

About 68% of the patients with TBTB develop some degree of bronchostenosis in the initial 4–6 months of the disease and up to 90% of patients have some degree of stenosis beyond this initial time period (2,4,5). Among patients with active disease involving the pulmonary parenchyma, 10–39% of patients are shown to have a component of TBTB (6). Initial treatment is a 4 drug regimen therapy as in pulmonary tuberculosis. However, due to a highly unpredictable disease progression when it involves the tracheobronchial tree, future interventions including bronchoscopic airway dilation or stent placement may be necessary.

Pathogenesis

Although the exact pathogenesis of TBTB is not well

understood, at least four different pathways are proposed leading to infection of tracheobronchial mucosa by mycobacteria tuberculi. Anyone or combinations of these pathways may lead to infections. In 1951, Smart proposed different methods of infection which included:

(I) Direct spread of tubercle bacilli from parenchymal tuberculosis or cavitary lesions containing abundant tubercle bacilli (7-10);

(II) Dissemination of tubercle bacilli from peribronchial lymphatic channels draining pulmonary parenchymal tuberculosis. This is supported by the finding that endobronchial biopsy in this patient population shows intact mucosa but submucosal involvement is noted on biopsy (7);

(III) Disease spread from contiguous mediastinal lymph nodes to the bronchial mucosa, occasionally resulting in Broncho nodal fistula. This mode of infection is particularly known to affect the pediatric population due to weaker airway walls and smaller airway diameter (11,12);

(IV) Direct implantation of inhaled mycobacterium tuberculosis into the bronchial wall mucosa (13).

TBTB can be clinically divided into active disease (bronchoscopic findings of active caseating material, ulceration or granulation tissue formation or histologic findings of caseating necrosis or a positive tubercle bacilli on culture) and fibrotic diseases (fibrosis seen on bronchoscopic view or biopsy-confirmed fibrostenotic tuberculosis often found to be culture negative) (7). During the healing phase of active endobronchial tuberculosis, cicatrization can cause mucosal ulceration, necrosis and fibrosis leading to stenosis (6).

Left bronchial involvement is seen more frequently than right bronchial or tracheal involvement (14). It is postulated that the left mainstem bronchus is anatomically compressed by the aortic arch and the left mediastinal lymph nodes tend to get infected faster than the right sided lymph nodes, resulting in increased vulnerability of the left main stem bronchus to endobronchial infection in TBTB.

Diagnosis

❖ Clinical symptoms: the prevalence of endobronchial tuberculosis is found to be twice as high in females as males. Lee and colleagues (6) hypothesized that female patient population tend to expectorate less frequently due to social customs and norms causing endobronchial stasis of the secretions and subsequent

infection. These women are usually found to be in their second and third decade of life (4,8,10,15,16). Presenting symptoms are variable, non-specific and insidious in onset. Cough is the most common presenting symptoms followed by sputum, weight loss, hemoptysis, chest pain and dyspnea (4,17). Not uncommonly patients are treated with antibiotics for bacterial pneumonia which proves inefficacious. Due to the non-specific symptoms, of TBTB alone, and its common coincidence with pulmonary/parenchymal disease, diagnosis is challenging and often delayed. In both the initial stages of solitary airway involvement of tuberculosis as well as in the late stages of TBTB, there have been reports of misdiagnosis of asthma in these patients (18). Wheeze and dyspnea are commonly reported particularly when patients develop bronchostenosis. Asthma, pneumonia and malignancy are often in the differential diagnosis of TBTB;

❖ The diagnostic yield of sputum examination is very variable. Despite best efforts and appropriate collection techniques a highly variable diagnostic rate of 13.6–53% is reported in patients with TBTB (2). Ozkaya *et al.* (1) reported on their experience with 23 patients with biopsy proven endobronchial tuberculosis all of whom were sputum smear negative. Such reports have ben indicative of a high false negative rate of negative sputum for acid fast bacilli in the diagnosis of TBTB;

❖ Tuberculin skin test was found to be positive in only 59.1% (2). Its lack of sensitivity in immunocompromised patients and lack of specificity due to its cross reactivity with non-tuberculous mycobacterium makes it an ineffective test to rule in or rule out pulmonary tuberculosis (2). Interferon gamma release assay (IGRA) has sensitivity of 64–92% but it cannot be relied upon to rule out or rule in pulmonary tuberculosis (19);

❖ Pulmonary function testing (PFT): The large airways contribute to approximately 50% of the total airway resistance (20,21). It is unclear what test most accurately quantifies the degree of upper airway obstruction. Spirometry typically shows limitation of maximal inspiratory and expiratory flows at high lung volumes. Miller and colleagues showed that lesions must narrow the tracheal lumen to <8 mm before symptoms occur (22-24). Moderate exercise limitation occurs when peak expiratory flow is reduced by about 40% and airway resistance is increased by about 600% (in which case FEV1 is still approximately 75% predicted). This limitation grossly corresponds to an upper airway
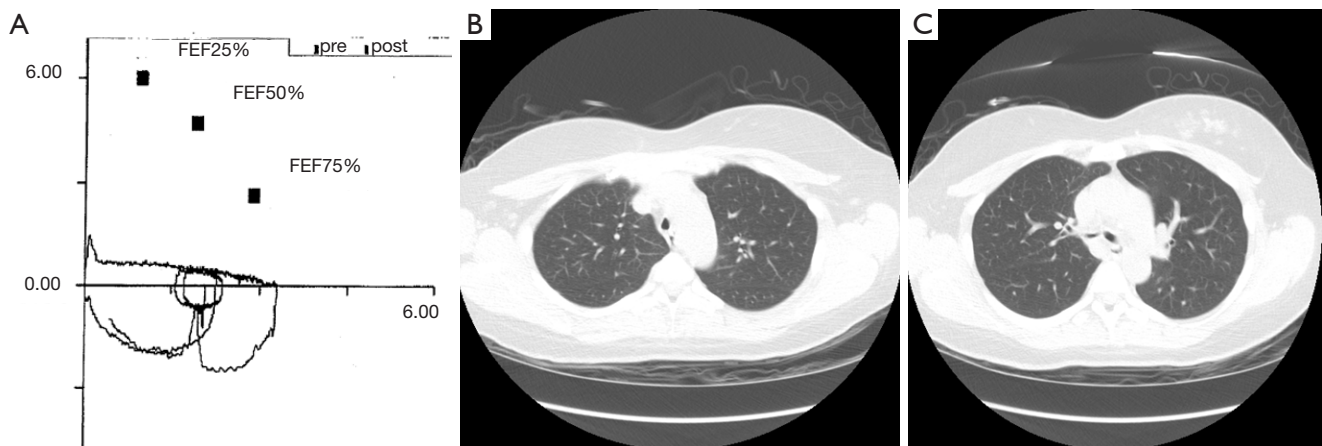
Figure 1 A 33-year-old South Korean female with history of treated TB, with 10 years diagnosis of asthma. (A) Flow volume loop with moderate flattening of the inspiratory and marked flattening of the expiratory limb; (B) distal tracheal stenosis with airway diameter of 8 mm; (C) right and left main stem bronchi stenosis measured 2.8 and 5.5 respectively.

that is narrowed to about 6 mm diameter. For all the reasons above, PFT tends to detect TBTB, after disease progression to the stage of fibrostenosis and significant central airway narrowing. If diffuse pulmonary disease accompanies TBTB, restrictive pattern disease may be present (25) (*Figure 1*);

❖ Chest imaging: chest imaging does not rule out endobronchial tuberculosis. Lee *et al*. (6) in a retrospective study found that 10% of the patients have normal chest X-ray. Pulmonary infiltrate is the most common findings seen on chest X-ray (18). In a study from south Korea (14) chest images of 121 patients with TBTB were reviewed. Seventy-one out of 121 patients (60%) had parenchymal infiltration while 24% had loss of volume. 8% of patients had cavitating lesions while surprisingly, 8% of patients had completely clear lung fields. Centrilobular nodules can be seen on CT of the chest. If patient develops tracheobronchial stenosis then depending on the airway involved, patient may have post-obstructive pneumonia or atelectasis in that region of the lung. CT imaging provides useful information about the extent of disease, length of bronchial involvement, any viable airway/lung parenchyma distal to the involved bronchus. Lee *et al*. (6) retrospectively looked at chest CT scans of 30 patients with lobar or complete lung atelectasis as a sequelae of TBTB in the setting of segmental, lobar or main stem bronchial stenosis. They concluded that chest CT scan can be useful in differentiating active TBTB from fibrotic stage disease. In active tuberculosis the bronchial

walls look edematous and irregular while fibrotic stage disease appears smooth with no significant airway wall thickening or edema;

❖ Bronchoscopic view: Chung *et al*. (26) reported on their detailed bronchoscopic examination of patients with TBTB and classified the bronchoscopic view of endobronchial tuberculosis to seven subtypes: actively caseating, edematous-hyperemic, fibrostenotic, tumorous, granular, ulcerative and nonspecific bronchitic. These morphological features have prognostic significance; With the exception of the tumorous type, Chung and Lee suggested that the clinical outcome of these subtypes can be predicted in the first 3 months of treatment. In actively caseating type, bronchial mucosa is hyperemic and diffusely covered with whitish cheese like material. In edematous hyperemic type the cheese like appearance is absent but edema causes some degree of airway obstruction without any evidence of fibrosis. Fibrostenotic type results in marked narrowing of the bronchial lumen with fibrosis. Tumorous type presents with endobronchial exophytic tumor covered with caseous material and results in near complete occlusion of the bronchial lumen. They described granular type as endobronchial lesions that resemble scattered grains of boiled rice. Visible ulceration of bronchial mucosa is seen in the ulcerative type. In non-specific bronchitic type only mild mucosal swelling and or hyperemia were seen on bronchoscopy. Actively caseating, edematous-hyperemic type and the fibrostenotic type are more

likely to proceed to bronchial stenosis despite treatment at 3 months. Frequently, healed endobronchial tuberculosis may leave black pigmentation within the airways. Multiple areas of black pigmentation can be seen on bronchoscopy. It is presumed that residue of mycobacterium tuberculosis leaves black pigments, a reportedly irreversible phenomenon (27).

Treatment

When treating endobronchial tuberculosis, two important goals are of utmost importance: eradication of tubercle bacilli and prevention of the most undesirable consequence, stenosis (28). While anti-tuberculous chemotherapy is efficient in controlling the infection, it does not appear to be a successful method in preventing residual TBTB (15,26,29) In a study done in South Korea Um *et al*. retrospectively looked at the predictors of persistent airway stenosis in 67 patients with microbiologically or histologically confirmed endobronchial tuberculosis that had completed anti-tuberculosis therapy. Patients received at least two bronchoscopies and endobronchial lesions were characterized as one of the seven subtypes originally described by Chung *et al*. (26). They reported the treatment outcome based on the degree of stenosis that was seen between the first and the second bronchoscopy, the second bronchoscopy was done at the completion of anti-tuberculous therapy. Persistent bronchostenosis occurred in 41.8% of the patients. In multivariate regression analysis, age >45 years, pure or combined fibrostenotic subtype and duration from onset of chief complaint to the initiation of anti-tuberculosis chemotherapy >90 days were identified as independent predictors of persistent airway stenosis. Oral corticosteroids (prednisolone equivalent >30 mg/d) did not reduce the frequency of persistent airway stenosis.

Chung *et al*. (26) reviewed 62 cases with actively caseating, edematous-hyperemic, fibrostenotic, and tumorous endobronchial tuberculosis all of whom showed luminal narrowing of the bronchus at diagnosis. Of these 62 patients, 43 patients continued to have endobronchial tuberculosis by the end of treatment; and despite appropriate treatment with anti-tuberculous therapy approximately 50% (22/43 patients) of the patients developed bronchostenosis. This pattern is consistent with other previous studies (30-32). Among 19 cases with granular, ulcerative, and nonspecific bronchitic endobronchial tuberculosis that did not show luminal narrowing of the bronchus at diagnosis, 17 cases healed

without bronchostenosis, while 2 cases of granular type still developed bronchial stenosis after treatment. They concluded that the evolution of endobronchial tuberculosis is determined by initial bronchoscopic findings and the subtypes.

Treatment of TBTB depends on the stage at which the diagnosis is made. In the active phase of the disease, the goal is to control the infection and prevent tracheobronchial stenosis. There is no clear evidence that any single mode of therapy can decrease the incidence of TBTB in this patient population (3). The following management strategies are proposed in the literature.

❖ Corticosteroids: corticosteroids have been used in children (33) and adults (3) without any benefit. As mentioned above, tracheobronchial stenosis is the most common long term complication despite adequate treatment. Um *et al*. (3) described 67 patients which were divided in two groups, patients who received steroids (37 patients, >30 mg equivalent prednisone/day) and the ones who did not receive steroids as part of the treatment. Both groups were treated with standard anti-tuberculosis therapy. The age, sex, smoking history, duration of treatment with anti-tuberculosis chemotherapy, pulmonary function test were similar in both groups. There was no difference in the outcome. Interestingly, patients who received steroids had symptoms longer than the group that did not receive steroids (155.8±27.3 *vs.* 67.6±8.3 days, P=0.004);

❖ Medical therapy: medical treatment is of no benefit in the fibrotic stage (3). Restoring the airway patency and relieving the symptom is the key to the treatment in fibrotic stage. Patients with TBTB caused by organisms known or presumed to be drug susceptible are treated in the same way as pulmonary tuberculosis. In general, antituberculous regimens consists of two phases: an intensive phase (2 months), followed by a continuation phase (4 to 7 months); most patients receive 6 months of treatment (intensive phase of 2 months and continuation phase of 4 months (34,35). Directly observed therapy (DOT) by enforcing compliance, has shown to improve the outcome in patients with pulmonary tuberculosis and thus decreasing resistance (34,35). However effect of DOT is not studied on patients with TBTB (4). As discussed earlier, Chung *et al*. showed that patients who received anti-tuberculous chemotherapy >90 days after diagnosis
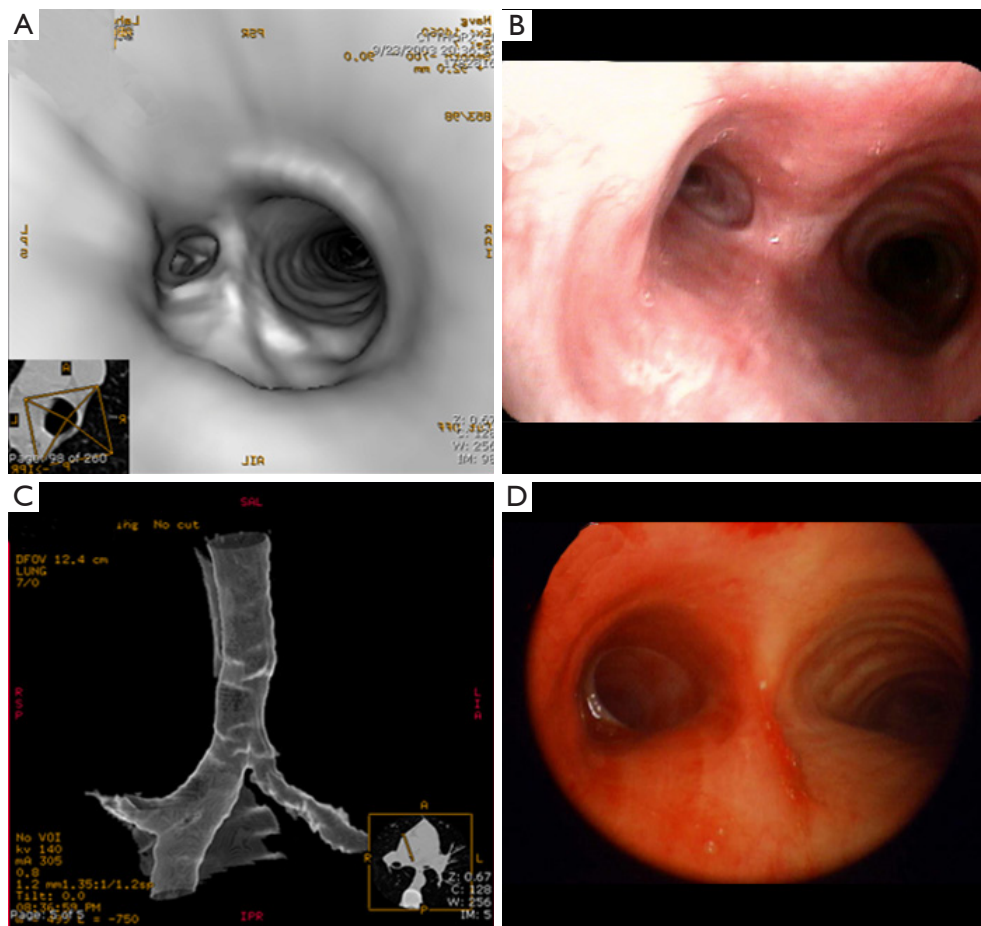
Figure 2 A 30-year-old female post multi drug treatments for pulmonary tuberculosis with persistent wheezing. (A,B) Long severe stenosis of the left main stem bronchus of chest CT scan with virtual bronchoscopy; (C) bronchoscopic view of left main stem stenosis; (D) airway patency obtained following airway dilation and silicone stent placement.

of tuberculosis and airway involvement, were more likely to develop persistent airway stenosis. This may suggest that medical therapy has a significant role in the progression of disease to fibrosis in the airway; however, there are no randomized trials that have looked at the effect of anti-tuberculous chemotherapy on TBTB progression;

❖ Bronchoscopic: in tracheobronchial stenosis, bronchoscopic intervention is not standardized and patients are treated on case by case basis depending on the symptoms, PFT, co-morbidity, chest imaging and bronchoscopic findings (3,26). Bronchoscopic techniques include balloon dilatation alone, stent placement following balloon dilatation, laser photoresection, argon plasma coagulation and cryotherapy (36-38) (*Figure 2*). Interventional

bronchoscopy has largely replaced surgical resection and bronchoplastic reconstruction which have been standard treatment in the past (29). Endobronchial ultrasound has been used to evaluate the underlying cartilaginous structure in the setting of tracheobronchomalcia in this patient population (38-40). It is recommended that patients with suspected tracheobronchial stenosis have an evaluation of the extent of their disease by pulmonary function tests with flow-volume loop followed by chest imaging when possible. Once subjective and objective data suggesting TBTB is obtained, patients will need flexible bronchoscopy and inspection of the airways. This can be done after anti-tuberculosis chemotherapy has completed. Endobronchial biopsy can be performed to rule out active endobronchial

tuberculosis at this time.

Iwamoto *et al.* (38) retrospectively assessed the efficacy of bronchoscopic techniques in treating airways stenosis in 30 patients due to TBTB. Twelve of 30 patients continued to have dyspnea, cough and repeated obstructive pneumonia due to tracheobronchial stenosis. One of 12 patients required pneumonectomy and the remainder underwent bronchoscopic interventions. The left main stem was the most involved site (8 patients). Tracheobronchial stents were inserted in 6/11 patients, 3 patients receiving silicone straight stents and the remaining three patients received silicone Y-stent. The remaining five patients only required balloon dilatation. There was significant improvement in symptoms in all patients. Minor complications including stent migration and granulation tissue were reported in the patients who had stent placement. The investigators did not report data on stent removal and long term follow up. As shown in this study, in about 30–40% of patients (38,41) balloon dilatation alone is sufficient. Radial endobronchial ultrasound is useful in examining the underlying cartilage, and any evidence of damaged cartilage warrants consideration of stent placement to support the airway as tracheobronchomalcia is a common finding in this patient population (38). Argon plasma coagulation, laser and cryoprobe can be used to remove the granulation tissue before or after dilatation and before stent placements.

When airway stenting is required, use of silicone stents is preferred. In the setting of benign airway stenosis such as TBTB, we recommend against the use of expandable metallic stents, particularly due to their increased risk of airway wall trauma and perforation, fatigue or rupture of the metallic stent and difficulty in retrieving the stent (39,40). Silicone stents instead are found to be removed easier and are less prone to granulation tissue formation. However, there are reports of self-expandable metallic alloy nitinol stents used for tuberculosis induced tracheobronchial stenosis (36-38,42).

Ryu *et al.* (36) in a retrospective study evaluated the role of bronchoscopic interventions including silicone stenting at a tertiary referral hospital in South Korea. Eighty patients underwent bronchoscopic intervention for the treatment of post tuberculous tracheobronchial stenosis over a period of 4 years. These interventions included balloon dilatation, neodymium-yttrium aluminum garnet laser resection as first line methods of airway dilation. The median luminal diameter was 9.5 mm in the trachea and 5 mm in bronchus when the lumen was measured by bronchoscopy.

Silicone stents were required in 75/80 (94%) patients.

Interventions were performed in patients who were symptomatic from post tuberculous tracheobronchial stenosis (progressive dyspnea, recurrent post-obstructive pneumonia or atelectasis of the lung or reduced lung function). There was a female predominance and median of 33 years of age and the most common involved location was the left main stem bronchus (65%).

Stents were removed in 54/75 (72%) patients after a median of 14 months. Fourthy nine of 54 patients had a successful stable clinical course during a follow up period of 36 months. However, 5 patients showed recurrence and needed re-stenting. These 5 patients along with remaining 18 patients (total 23 patients) required prolonged stent placement (median 32 months). Three patients showed no response to bronchoscopic intervention and needed surgical resection involving end to end anastomosis. During a median follow up period of 41 months, clinical outcome was unchanged in all patients.

Subgroup analysis between those who had their stents successfully removed and those who continued to have stents showed that patients with prolonged stent placement had a lower baseline FEV1 and need for more re-intervention. Granulation tissue and re-stenosis were also more common in patients who required re-stenting and those stented for longer duration.

Minor complications such as cough, mucus plugging and blood tinged sputum was seen in majority of the patients. Eight of 80 (10%) patients experienced major complications which included massive bleeding leading to respiratory failure and requiring blood transfusion and mechanical ventilation, Pneumothorax occurred in five patients and pneumomediastinum in two patients and there was no mortality.

Similarly, Wan *et al.* (43) published their experience with silicone stents in patients with tuberculosis-induced tracheobronchial stenosis over 7 years. Seven patients with a mean age of 43 years underwent a total of 11 dilatations with placement of 10 straight stents and 1 Y stent. Stents were left in situ for a mean of 32 months. One patient had pneumothorax and two patients had migration of the stents requiring stent revision. There was no mortality. These and other studies conclude that silicone stents are safe in the management of patients with tuberculosis-induced tracheobronchial stenosis (36). There are no definite guidelines on the required duration of stent placement in the airway. Based on published data from investigators in high prevalent areas with tuberculosis, an attempt can be made to remove stents in 8–16 months after placement

(36,44). These studies highlight the role of advanced therapeutic bronchoscopy procedures in the management of chronic fibrostenosis in the central airways following tuberculosis and anti-tuberculous therapy. Airway stent placement can serve as a temporary therapeutic intervention followed by successful stent removal with no need of re-intervention.

Conclusions

TBTB can present with and without evidence of parenchymal disease on imaging. The course of the disease in unpredictable but delay in medical therapy is shown to increase the likelihood of progression to fibrostenosis. Early diagnosis and treatment is often missed due to its varied clinical presentation. Patients with pulmonary tuberculosis presenting with continued respiratory symptoms after treatment should be evaluated for tracheobronchial stenosis. Interventional bronchoscopic approaches should be considered to restore airway patency.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Tracheobronchial tuberculosis: a clinical review

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Abstract: Endobronchial tuberculosis (EBTB) is defined as tuberculous infection of the tracheobronchial tree. The exact pathogenesis is unclear, and it has a heterogenous clinical course. Its diagnosis requires the clinician to have a high index of suspicion based on clinical symptoms and radiological features. Computed tomography and bronchoscopy are useful tools in its evaluation. The goal of treatment is in the eradication of tuberculous bacilli with appropriate anti-tuberculous therapy. Use of corticosteroids is controversial for the prevention of tracheobronchial stenosis. Interventional bronchoscopy or surgical intervention is employed to restore airway patency once significant stenosis occurs.

Keywords: Endobronchial; tracheobronchial; tuberculosis (TB); bronchoscopy; stenosis

Introduction

Tuberculosis (TB) remains a heavy global health burden. The 2015 Global WHO TB report mentions an estimated 9.6 million incident TB cases, which was a considerable increase compared to estimates from 2014 (1). Of TB cases, patients with endobronchial tuberculosis (EBTB) often face a delayed diagnosis. EBTB is defined as a tuberculous infection involving the tracheobronchial tree. Its exact pathogenesis is unclear. However, postulations include: (I) direct infiltration of disease from the lungs; (II) infected sputum/secretions causing direct implantation of organisms; (III) haematogenous spread; (IV) lymphatic dissemination; and (V) erosion of lymph nodes into the trachea or bronchus (2). EBTB has complex and varying clinical courses and continues to bear a heavy health burden due to the severe sequelae of bronchostenosis.

Clinical and radiological features

EBTB appears to have a preponderance in females in their second and third decades of life (3,4). Van de Brande *et al.* have described EBTB in an elderly population as well with a mean age of 70 years (5). Symptoms include a productive cough, chest pain, haemoptysis, lethargy, fever and dyspnea (3). Clinical findings are heterogeneous, and can include a focal wheeze and decreased air entry on auscultation (3). Because the signs and symptoms are non-specific, the diagnosis of EBTB should be made with a combination of clinical suspicion, clinical findings, and radiology and sputum/tissue analyses.

Chest roentgenograms (CXR) may appear normal unless there is significant airway obstruction leading to atelectasis of the distal pulmonary segment, or concurrent parenchymal or pleural disease (*Figures 1,2*). Computer tomography (CT)

Figure 1 Chest roentography showing atelectasis of left lung with partial aeration of left upper lobe.

Figure 2 Right bronchus intermedius stenosis resulting in middle and lower lobe collapse.
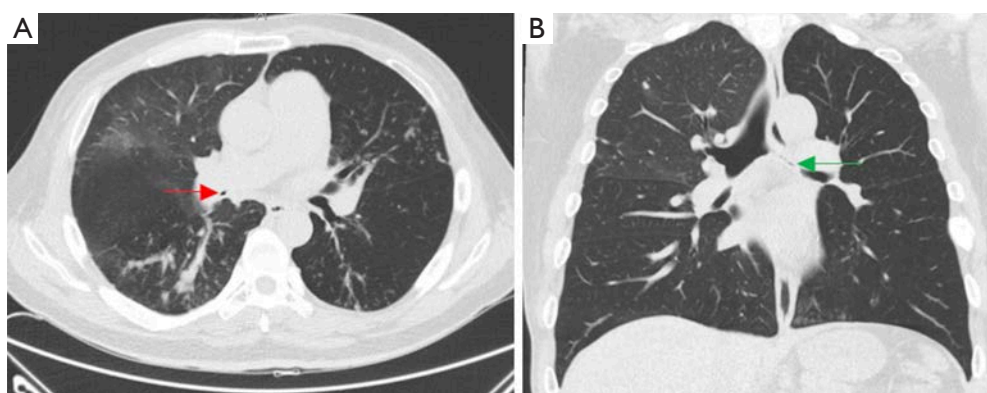

Figure 3 CT thorax showing left main bronchus (red arrow) and right bronchus intermedius stenosis (green arrow), with distal tree-in-bud infiltrates.

of the thorax would yield more detail such as irregularities/stenosis of the airways, as well as other features of TB in the thorax such as mediastinal lymphadenopathy, nodules, cavities and pleural effusions (*Figures 3,4*). Furthermore, a 3-dimensional (3D) reconstruction of the airways (*Figure 5*) allow for estimating the extent of airway narrowing, and help plan for further intervention such as bronchoscopy as well as surgery (6).

Contrary to clinical expectations, sputum analysis in EBTB has variable diagnostic yield, with reports from 17% to 79% if combined with specimens obtained via bronchoscopy (7,8). Postulations to this include the lack of ulceration in the mucosal wall of the bronchus, or difficulties in expectoration (9). As such, adjunct methods

such as nucleic amplification tests are now increasingly used to help detect TB and aid in more rapid diagnosis (10).

Endoscopic and histopathologic findings

EBTB tends to affect the right upper and right main bronchi (7), though any part of the tracheobronchial tree can be afflicted. It is well-described to take on different endoscopic appearances. A comprehensive study done by Chung *et al.* has described the following subtypes: (I) actively caseating (*Figure 6A*); (II) oedematous-hyperaemic (*Figure 6B*); (III) fibrostenotic (*Figure 6C*); (IV) tumorous (*Figure 6D*); (V) granular (*Figure 6E*); (VI) ulcerative (*Figure 6F*); and (VII) nonspecific bronchitis (*Figure 6G*) (10).
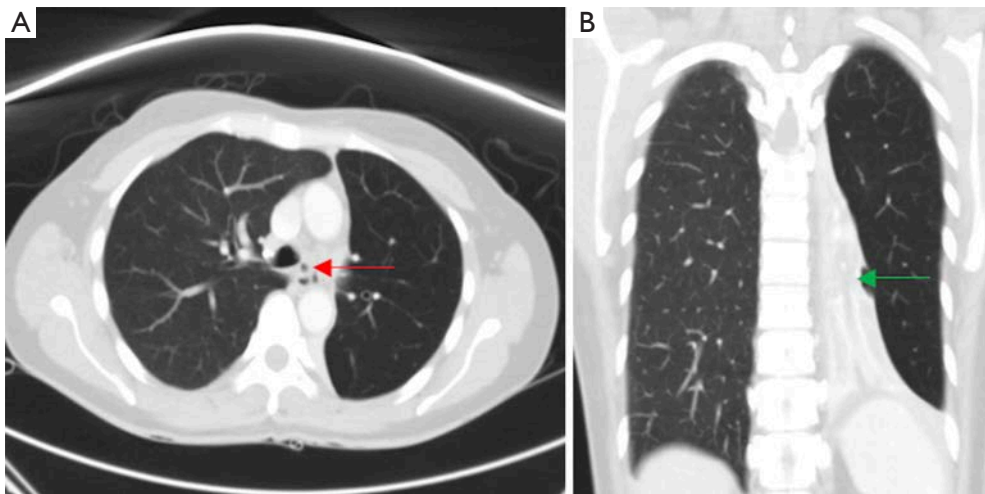
Figure 4 CT Thorax showing left main bronchus narrowing (red arrow) and resultant distal atelectasis (green arrow).
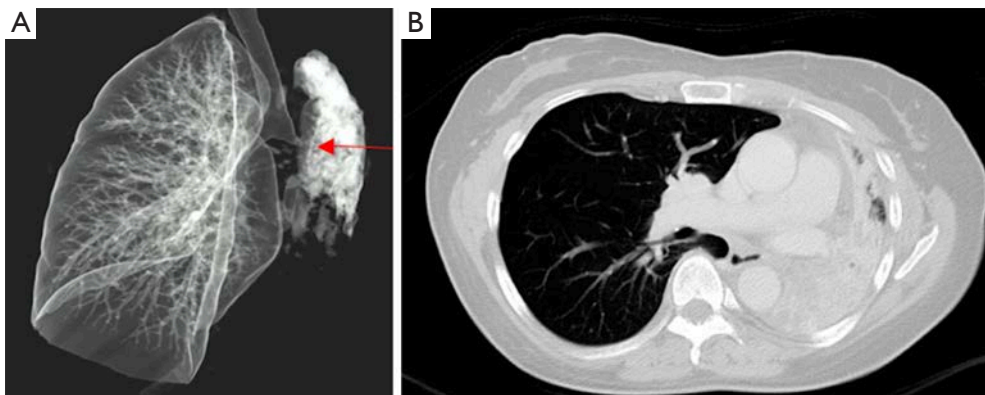

Figure 5 3D-reconstruction of airways showing stricture of left main bronchus (red arrow) and resultant distal atelectasis.

Interestingly, the tendency to develop bronchial stenosis could be predicted from bronchoscopic appearances of the mucosa. Oedematous-hyperaemic, fibrostenotic, and tumorous subtypes tended to progress to eventual bronchial stenosis/obstruction within 3 months despite appropriate treatment (10). On analyzing bronchial lavage fluid samples, the granular subtype seemed to yield highest smear and culture positivity for *Mycobacterium tuberculosis*, whereas both tests were negative for the fibrostenotic and nonspecific subtypes (11). The presence of caseating granulomas or acid fast bacilli (AFB) would cement the diagnosis of EBTB.

The above classification of EBTB can be explained by evolution of the disease. The initial lesion, with lymphocytic infiltration of the submucosa, is characterized by simple erythema and oedema of the bronchial mucosa. This would correspond to the nonspecific bronchitis subtype. With the formation of submucosal tubercles, a more granular appearance develops (the granular subtype). Subsequent oedema and erythema gives rise to the oedematous-hyperaemic subtype. At this stage, the oedema can result in bronchial stenosis. From here, the lesion can undergo caseous necrosis with tuberculous granuloma formation on the mucosa (leading to the actively caseating appearance). If the inflammation persists and breaches the mucosa, an ulcer is formed, giving rise to the ulcerative subtype. Rikimaru *et al.* further described three stages of bronchial ulcers (12): (I) active stage or Stage A which were only observed before TB treatment commenced; (II) healing stage (Stage H) and scarring (Stage S). The mucosal ulcer can further evolve to form hyperplastic, inflammatory polyps, forming the
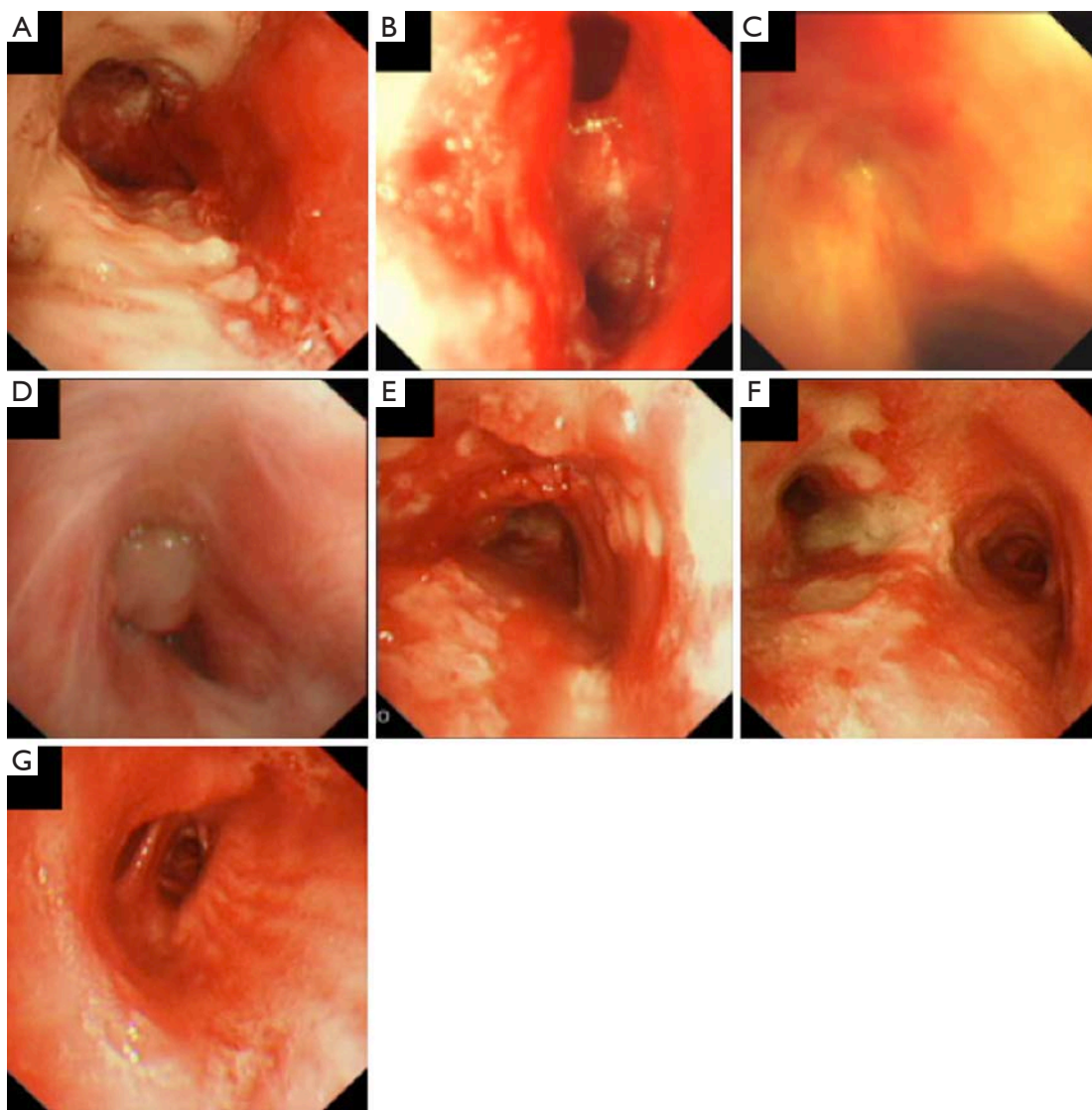
Figure 6 Bronchoscopic appearances of endobronchial TB. (A) Actively caseating; (B) oedematous-hyperaemic; (C) fibrostenotic subtype; (D) tumorous subtype; (E) granular subtype; (F) ulcerative subtype; (G) nonspecific bronchitic subtype.

tumorous subtype. Ultimately, the endobronchial lesions would heal via fibrostenosis (6,11).

Management

Interactions of EBTB with host immunity, antituberculous treatment and the effects of mycobacterial infection lead to a heterogenous clinical course.

For active disease, the two goals of treatment are eradication of the tuberculous bacilli, as well as mitigating development of tracheobronchial stenosis, although stenosis can occur despite timely treatment with antituberculous drugs (7). A systematic review and meta-analysis by Critchley *et al.* showed that steroids could be effective in mortality reduction in all forms of TB (13). Nemir *et al.* (14) found prednisone as an advantageous addition to lymph node TB therapy if given within four months of the course of illness. However, specific to EBTB, the routine use of corticosteroids remains controversial. Shim (15) proposed steroid therapy for the oedematous-hyperaemic, caseating and tumorous subtypes. The suggested dose was prednisolone 1 mg/kg for 4–6 weeks followed by slow taper over a further 4–6 weeks. Conversely, a prospective study of 34 adult patients using corticosteroids in the treatment
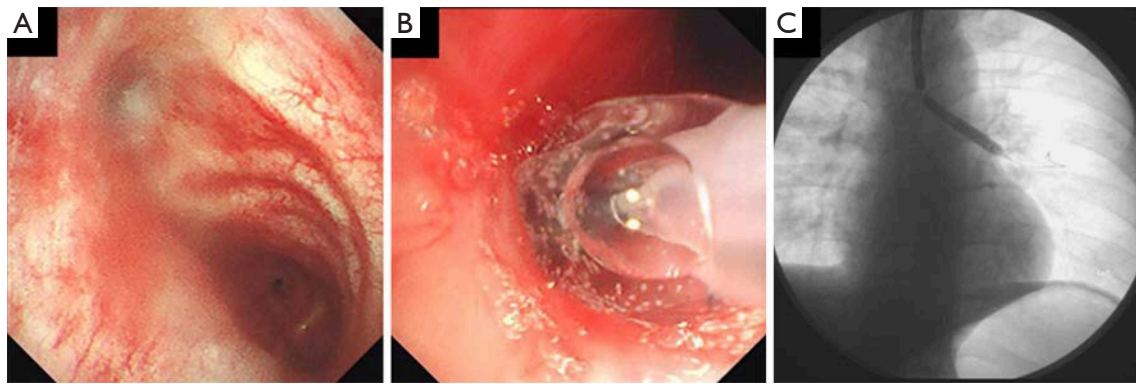
Figure 7 Balloon dilation of left main bronchus stricture. (A) Stricture before dilation; (B) balloon dilation in progress; (C) fluoroscopic view of balloon and guidewire in left main bronchus.

of EBTB showed no significant difference in healing rates that were observed bronchoscopically, and that treatment did not affect pre-existing fibrotic lesions (16). Similarly, a retrospective study by Um *et al.* (17) did not find additional benefit in the addition of prednisolone to prevent airway stenosis for patients with proven EBTB.

Patients who suffer from bronchial stenosis leading to distal obstruction and atelectasis often present with wheezing (which can be localised on auscultation) and dyspnoea. Treatment modalities to restore patency of the airways include bronchoplasty and surgery.

Bronchoplasty via interventional bronchoscopy allows for the application of various techniques such as balloon dilatation (*Figures 7A,B*), argon plasma coagulation, laser, electrosurgery and cryotherapy; these methods can be applied either singly or in combination to achieve the desired results (8,18-20). Cho *et al.* (19) performed balloon dilatations on 113 EBTB patients with tracheobronchial strictures and reported a 73% success rate, after single or multiple dilatations.

Various factors can influence the success of balloon dilatation. Cho *et al.* (19) encountered treatment failure in 27% (n=31) of patients who had undergone balloon dilatation, with recurrence of symptoms between 1 day to 113 months with a mean of 13 months. All patients had been receiving antituberculous therapy for a minimum of 5 months. For the patients who failed to respond to balloon dilatation, alternate measures such as a temporary stent, cutting balloon dilatation, radiation-eluting balloon dilatation or surgical measures were explored. He found a longer stricture length tended towards a shorter patency period post balloon dilatation, and suggested using a larger balloon diameter (up to 12 mm for bronchial strictures and

20 mm for tracheal strictures). Silicon stents (*Figure 8*) can be inserted into the airway once recanalised to maintain patency, whereas metallic stents should be used very cautiously due to overgrowth of granulation tissue as well as mechanical complications such as stent fracture (19-22). Other complications related to balloon dilatation as well as stenting include airway wall perforation, stent migration leading to obstruction, and haemoptysis (21).

A retrospective study looking at CT features as predictors of outcome after endobronchial interventions (including balloon dilatation, stenting and surgical bronchoplasty) in patients with EBTB found the presence of parenchymal calcification, and bronchiectasis within atelectasis had a higher tendency towards failure. Interestingly, mucus plugging, extent of airway narrowing and volume loss on CT images did not affect patient outcomes after expansion procedures (23).

Surgery is considered when interventional bronchoscopic measures fail. Lobectomy or pneumonectomy has been well-established (*Figure 9*). Other methods such as sleeve resection, carinal resection, reconstruction of the bronchus or trachea and end-to-end anastomosis have been used to treat post-tuberculous airway stenosis (24-26).

Conclusions

EBTB presents with non-specific, insidious symptoms. There must be a high index of clinical suspicion, and its diagnosis should be supported by radiological and bronchoscopic appearances as well as microbiological/histopathological evidence. The mainstay of treatment remains to be antituberculous chemotherapy. The role of corticosteroids is controversial, and even with
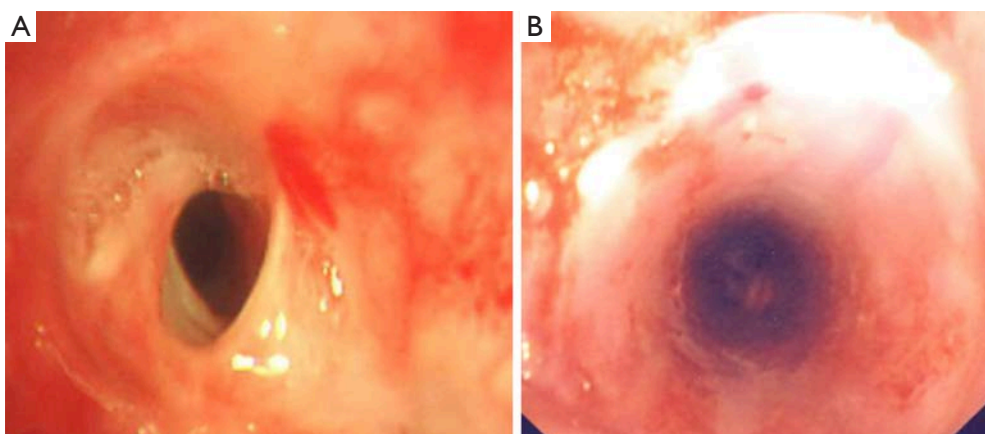
Figure 8 Fibro-stenotic left main stricture (A), radial cuts applied with electrosurgical knife, dilated with balloon bronchoplasty (not demonstrated), and silicon stent placement (B).
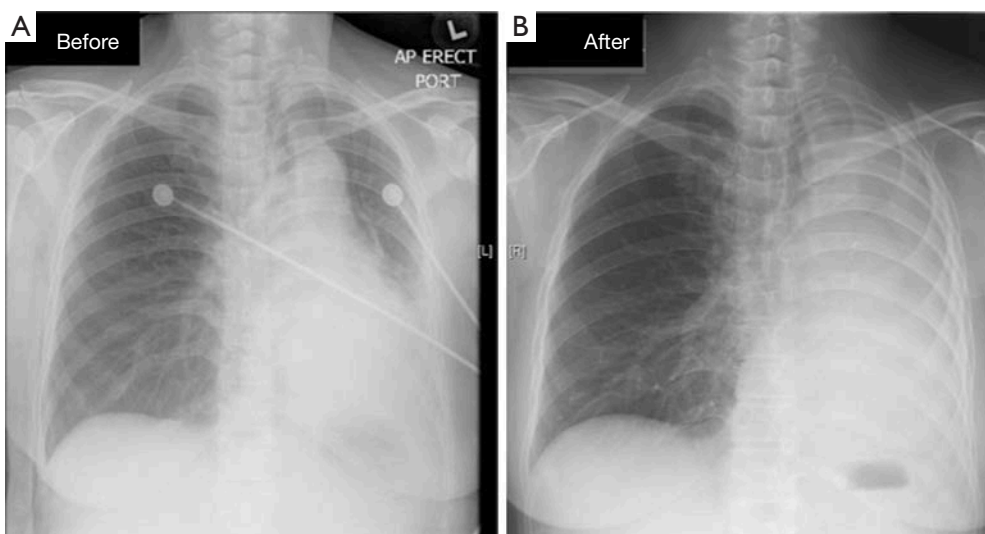

Figure 9 Before and after left pneumonectomy for post tuberculous endobronchial stricture, after failing balloon dilatation of left main bronchial stricture.

timely treatment, some patients eventually progress to tracheobronchial stenosis. CT with 3D reconstruction of the airways allow for better planning of bronchoscopic or surgical procedures. Bronchoscopic-guided balloon dilatation can be done as a single procedure, or may require repeated staged events, and might be used in combination with other tools such as electrocautery, argon plasma coagulation, laer, or cryotherapy. Stents, preferably silicone stents, may be inserted to maintain airway patency. Should these measures fail, surgical options can be explored to help patients with debilitating stenosis.

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Evolutional trends in the management of tracheal and bronchial injuries

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Abstract: Tracheal and Bronchial injuries are potentially life threatening complications which require urgent diagnosis and therapeutic intervention. They typically occur in association with blunt and penetrating chest trauma although they are increasingly being encountered in patients following endobronchial intervention and percutaneous tracheostomy insertion. Their precise incidence is unknown. Presenting features include dyspnoea, stridor, respiratory and haemodynamic compromise, haemoptysis, surgical emphysema, pneumothorax and persistent significant airleak. There may be other additional injuries to consider in trauma patients with large airway injury. Familiarity with the diagnosis and management of large airway injuries is important for medical teams engaged in emergency medicine, thoracic surgery and medicine, anaesthesia and intensive care. Although early surgical intervention is the mainstay of treatment, endobronchial manoeuvres to seal defects are receiving increasing attention particularly for patients with medical co-morbidities which may contraindicate formal surgery or transfer or where local surgical expertise is not available.

Introduction

Tracheal and tracheobronchial injuries are rare, but serious consequences of blunt trauma, penetrating wounds and iatrogenic injuries associated with endotracheal intubation and mechanical ventilatory support and with endobronchial intervention including airway dilatation (1-3).

The incidence of these complications is not known, although a study reported a total of 1,033 tracheal injuries over a 5-year period in Germany (1). A total of 429 of these were non-iatrogenic (blunt trauma 276, penetrating wounds 94, bullet wounds 16, other aetiologies 43) and 604 of these injuries were iatrogenic (endotracheal intubation/ mechanical ventilation 372, dilatational tracheostomy 181, endoscopic interventions 51). Another study reviewed the world literature on blunt intrathoracic tracheobronchial injuries and identified 265 patients (4).

Blunt trauma is a major cause of death from thoracic trauma (4). Although it is believed that over 80% of patients who sustain blunt traumatic tracheal or bronchial injury die before arriving at hospital (5,6), post-mortem findings suggest an incidence of 2.8% of tracheobronchial injuries in patients who die following blunt chest trauma (7). Often, the right main bronchus is affected more than the left perhaps as a consequence of relative protection of the left main bronchus afforded by the aorta (8).

Tracheobronchial injuries can be transverse between tracheal rings or may be longitudinal or spiral across the membranous portion of the trachea and main bronchi or indeed may present with a combination of both type of injuries (9).

Typically, in iatrogenic injuries, a longitudinal running defect in the posterior wall is encountered (1,10-13). This may be more common, in my opinion, when a bougie is employed for patients when endotracheal tube insertion is difficult.

It is appreciated that although tracheobronchial injuries are rare, the number of patients who sustain these injuries

Table 1 Causes, presentation and diagnosis of tracheal and bronchial injury

Aetiology
Thoracic trauma
Blunt
Often within 2.5 cm of carina
High mortality
May be associated with posterior dislocation of sternoclavicular joint
Penetrating
Bullet and knife wounds
Iatrogenic
Percutaneous tracheostomy
Endotracheal intubation
Mechanical ventilation
Dilatation of stricture
Endobronchial laser therapy
Clinical presentation
Clinical features
Dyspnoea
Stridor
Haemoptysis
Subcutaneous emphysema
Tension pneumothorax
Persistent or large air leak
Flail chest
Diagnosis
High index of suspicion depending on the nature of the insult
Chest radiography
Thoracic CT (to include trachea)
Bronchoscopy

will be encountered more frequently in clinical practice. This will reflect the increasing numbers of patients who sustain traumatic injuries in the community who survive to hospital admission, thanks to improved pre-hospital medical care. Furthermore, with the expanding development of percutaneous tracheostomy techniques in intensive care units and the expansion of endobronchial intervention

services worldwide, it is likely that further iatrogenic injuries will occur (14.15). Therefore, familiarity with techniques to successfully manage these patients among Surgical, Emergency Medical and Intensive Care Teams and Anaesthetists is becoming increasingly important.

Diagnosis

It is important to have a high index of suspicion for tracheobronchial injuries among patients who have sustained thoracic injury (blunt on penetrating) or who may have experienced iatrogenic injury at the time of endotracheal intubation/mechanical ventilation or following large airway intervention (*Table 1*).

Typical clinical features will include stridor, dyspnoea, haemoptysis, subcutaneous emphysema, tension pneumothorax and persistent or large air leak, which will mandate the deployment of one or more chest tubes or indeed urgent surgical intervention. The patient may have a flail chest.

Routine investigations include chest radiography, thoracic CT scan (to include the trachea) and bronchoscopy. In patients who have non iatrogenic traumatic injury it must be appreciated that other injuries may co-exist, e.g., to the oesophagus, lung parenchyma, heart and great vessels, brain, abdomen etc. Injuries are diagnosed and prioritised and several teams may be involved in patient management.

Rigid and flexible bronchoscopy is used to confirm the diagnosis of the injury and to determine its extent and to define its anatomy. High-frequency jet ventilation or low tidal volume using a Sanders injector is given to minimise additional airway injury and subcutaneous emphysema while the airway injury is inspected and defined (10-13,16,17). While considering treatment strategies, the rigid bronchoscope is passed beyond the injury and a Bougie is deployed in the main bronchus. The rigid bronchoscope is removed and an endotracheal tube is inserted over the Bougie to ensure that it bypasses the defect. The position of the tube is then confirmed with a flexible bronchoscope. It may be necessary to consider deployment of a dual-lumen endotracheal tube depending on the location and extent of the airway injury.

Treatment options

Surgery

As these complications are rare, it is quite possible that the attending teams may not have the surgical capabilities to

manage these patients. Under such circumstances, prompt early discussion with Specialist Centres and urgent transfer if and when the patient is deemed suitable for surgical intervention should be made. However, it may be that the patients have other significant comorbidities which would render their tolerability of formal surgical intervention prohibitive or transfer may not be possible and therefore other avenues may have to be pursued.

Surgical approaches include thoracotomy, sternotomy, clamshell incision and cervical incision. For tracheal separation, previous authors have described passing the endotracheal tube across the lacerated trachea and completing the repair over the endotracheal tube and this has also been used for incomplete tears. For main bronchial lacerations, selective intubation of the non-injured main bronchus is usually performed and injuries are repaired completely. A variety of different techniques to surgically manage these patients has been described (1-8,18-21).

Techniques described for managing complete tracheal transection involve passing an endotracheal tube across the injured area and completing the repair over the tube. A dual lumen tube or selective intubation of the injured side can be used to manage patients with a main bronchial injury (18). The same approach has been used in both blunt and penetrating injuries. Primary repair with end to end anastomosis using non-absorbable (e.g., Prolene) suture is preferred for circumferential injury. Perioperative sepsis must be aggressively managed. Devitalised tissue is removed, primary closure without tension is performed and vascular supply to the wound edges is preserved as much as possible (19). Postoperative airway stenosis (18) or dehiscence may occur. Surgical mortality of 4–30% has been reported (18-21) and early surgical intervention (within two hours of trauma) may influence outcome (18). Mortality appears to be higher among patients with blunt rapture (18). However, these injuries are rare and not all surgeons have ongoing still in their management. Furthermore patients may have other diverse injuries within the confines of their trauma which may influence outcome. This must be borne in mind when considering the indications for, and outcomes of, surgery.

Endobronchial techniques

It is not always possible to perform primary surgical repair either because of coexistent comorbidities, multiple associated trauma injuries, patient instability to facilitate transfer or lack of local expertise. Under such circumstances, endobronchial manoeuvres are being increasingly explored. A rigid and flexible bronchoscope can be inserted into the airway and ventilatory support can be applied as described above. A covered expandable metallic stent can be inserted into the airway and an endotracheal tube (or if appropriate a tracheostomy tube) can be positioned to lie within the stent using a fiberoptic bronchoscope. The fiberoptic bronchoscope is passed through the endotracheal tube or the tracheostomy tube and is then inserted into the stent allowing for the definitive airway to be placed with confidence into the centre of the stent over the bronchoscope itself (22). We have had encouraging experience in managing patients in this fashion, where the stent has acted as a scaffold to promote tissue healing. Bronchial toilet is essential and antibiotic therapy is prescribed to provide prophylaxis against or to treat intercurrent infection with close ongoing communication with microbiologists and prospective microbiological surveillance.

For tears, less than 5 mm diameter, it may be possible to seal the defect by direct application of BioGlue (CryoLife Europa, UK) applied directly using pledgets (23).

Over the past 5 years, 10 patients were referred to our unit with traumatic or iatrogenic tracheal tears. All patients were managed by the cardiothoracic intensive care unit team. Formal surgical repair was contraindicated for each patient on account of significant medical co-morbidities. Five patients were treated with endotracheal stenting (3 patients) and with the application of Bio Glue (2 patients). Four (80%) of these patients survived. The other five patients had sustained a large tear (>2 cm length) and were managed conservatively. Three of these patients died of sepsis and 2 (40%) survived.

Conclusions

Although rare, it is believed that an increasing number of patients with tracheal and bronchial injuries will be seen in hospital as a consequence of improvement in prehospital medical care and the expansion in percutaneous tracheostomy insertions and large airway intervention techniques. Thus increasing awareness of the aetiology, diagnosis and management of patients with these complications is necessary for emergency medical and surgical teams, anaesthetists and these involved in intensive care. Traditionally surgical intervention has been the main management strategy but the encouraging results of endobronchial techniques suggests that such an approach

should be considered for all high-risk candidates with tracheal defects in the region of 1.5 cm or less.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Colobronchial fistula: the pathogenesis, clinical presentations, diagnosis and treatment

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Background: Colobronchial fistula (CBF) is rare and easy to be delayed in clinic. There is no systemic study about this disease. The pathogenesis, clinical presentations, diagnosis and treatment of CBF were analyzed in this study.

Methods: The clinical data from 37 cases of CBF, which included one case in our institute and the other 36 cases in literature from January 1960 to August 2016, were reviewed and analyzed. The etiology, clinical presentations, diagnostic and therapeutic methods, and outcomes were summarized.

Results: The causes of CBF included Crohn's disease, postoperative intraperitoneal adhesion, diaphragmatic hernia, pulmonary infection or abscess, colonic malignancy, colonic interposition, radiation, hyperthermic intraperitoneal chemotherapy (HIPEC), diaphragmatic mesh repair, pulmonary tuberculosis and pyonephrosis. Based on the anatomical location and the causes of fistula, CBF were divided into four types: type I, CBF secondary to the adhesion among colon, diaphragm and lung; type II, CBF secondary to diaphragmatic hernia; type III, CBF secondary to sub diaphragmatic abscess or emphysema; type VI, CBF secondary to colon interposition. The characteristic clinical presentations of CBF was productive cough with foul smelling sputum (78.38%), most of the patients were finally confirmed the diagnosis by barium enema or water-soluble contrast enema study (67.57%) and computed tomography (CT) scan/with multiplanar reconstruction (16.22%); 35 cases (94.59%) accepted the surgical treatment. Among 31 patients with recorded follow-up data, 26 patients recovered unevenly, but 5 patients died in 1 month after treatment.

Conclusions: CBF is a rare but can not be ignored disease. Anything which may induce the direct or indirect connection between colon and lung tissue may result in CBF. Productive cough with foul smelling sputum is the characteristic symptom. Radiological investigations such as barium enema and/or CT scan with multiplanar reconstruction are valuable for the confirmation of CBF. Surgery based on the etiology is the foundation of treatment.

Keywords: Bronchus; colon; fistula; diagnosis; therapy

Introduction

The fistula between respiratory system and digestive tract is not uncommon in clinic. Owning to the different anatomy and physiological function of respiratory system and digestive tract, the fistula between these two systems usually cause severe clinical outcome and need to be diagnosed and treated in time. The most common fistula between respiratory system and digestive tract is tracheal or bronchial esophageal fistula. However, colobronchial fistula (CBF) [or colono pleuro bronchial fistula (CPBF)] is rare in clinic (1-5). Only 36 cases were reported from January 1960 to August 2016 in literature. So far, there is little information for this disease. CBF usually has complicated clinical presentations and is easily delayed. So, it is necessary to systemically study this disease to further improve the diagnosis and treatment of this disease.

In this study, the data from a total of 37 cases, one treated in our institute and the others reported in literature, were summarized and analyzed in order to get a comprehensive understanding of this rare disease.

Methods

A case of CBF in our institute

A 41-year-old man was admitted to our department with a one month history of productive cough with foul smelling sputum. He suffered a traffic accident 10 years ago where he had left ribs fracture. The patient was discharged after treatment in local hospital. Four years ago, he felt abdominal pain and distension without any causes. An acute appendicitis was diagnosed and an appendectomy was performed in local hospital. No obvious intestinal obstruction was found during operation. After operation, the patient recovered well until the 8th day a paroxysmal cough with yellow sputum appeared. The patient was diagnosed as pneumonia and was discharged after treatment with antibiotics. But since then, the patient had occasional cough with sputum and had lost 10 kg in weight. One month ago, he felt dyspnoea and severe productive cough with foul smelling sputum, and some fecal material appeared in the sputum.

After admission, a chest X-ray revealed an infiltration in the left lower lobe. Barium meal and follow-through study followed by a computed tomography (CT) scan with multiplanar reconstruction showed consolidation in the left lower lobe, left pleural adhesions, the splenic flexure herniated into left chest cavity and there was a suspected

connection exist between the splenic flexure and the left lower lobe (*Figure 1A,B*). At bronchoscopy, mucopurulent secretions were observed from the left lobe. In order to avoiding the barium was flushed into bronchus, a colonoscopy was performed instead of the barium enema. At colonoscopy, there was a dead-end found in the splenic flexure and a fistula was found in this dead-end (*Figure 1C*), which further confirmed the fistula existed between colon and bronchus.

A left exploratory thoracotomy was performed. It was found that there was a 5 cm rupture in the left diaphragm, the splenic flexure herniated into left chest cavity and tightly adhered to left lower lobe. A fistula existed between lower lobe and the splenic flexure. The left low lobe was consolidated and couldn't expend after recruitment. A left lower lobectomy was performed and the fistula was removed. The colon was sutured and the left diaphragm was repaired. The patient fully recovered and was discharged from hospital 14 days later. He was uneventful after 5 years follow up. The review of the patient's information was approved by the review board of Tangdu Hospital.

Clinical data

By searching in PubMed database, China Academic Journal Network Publishing Database and using Google research engine (restricted in English and Chinese papers), the published CBF cases (36 cases) from January 1960 to August 2016 were collected. All clinical data from the total of 31 cases (age: 11–73 years; male *vs*. female: 19 *vs*. 18 cases) were reviewed and analyzed. The etiology, characteristic clinical presentation, diagnostic and treatments methods, and outcomes were summarized.

Results

The causes of CBF

The causes behind CBF included Crohn's disease, postoperative intraperitoneal adhesion, traumatic and un-traumatic diaphragmatic hernia, pulmonary infection or abscess, colonic malignancy, colonic interposition, radiation, hyperthermic intraperitoneal chemotherapy (HIPEC), diaphragmatic mesh repair, pulmonary tuberculosis and pyonephrosis (*Table 1*). Based on the anatomical location of fistula and different causes, all the CBF cases were classified into four different types. Type I, CBF secondary to the adhesion among colon, diaphragm and lung (20 cases)

Figure 1 The CT and colonoscopic appearance of colobronchial fitula. (A,B) CT scan with multiplanar reconstruction showed consolidation in the left lower lobe, left pleural adhesions, the splenic flexure herniated into left chest cavity and there was a suspected connection exist between the splenic flexure and the left lower lobe; (C) at colonoscopy, there was a dead-end found in the splenic flexure and a fistula was found in this dead-end (black arrow). CT, computed tomography.

Table 1 The classification and causes of colobronchial fistula

Classification and causes	N (%)	References
Type I	20 (54.05)	
Crohn's disease	6	(1,6-10)
Colonic malignancy	3	(11-13)
Postoperative intraperitoneal adhesion	4	(14-17)
Abdominal radiation	1	(18)
Diaphragmatic mesh repair	1	(5)
Tuberculosis	1	(19)
Pulmonary infection or abscess	4	(17,20,21)
Type II	8 (21.62)	
Traumatic diaphragmatic hernia	4	(22-24), our case
Un-traumatic diaphragmatic hernia	4	(2,3,17,24)
Type III	7 (18.92)	
Postoperative intraperitoneal adhesion	3	(25-27)
Crohn's disease	2	(2,28)
HIPEC	1	(29)
Pyonephrosis	1	(30)
Type IV	2 (5.41)	
Colonic interposition	2	(31,32)

N, number of patients; HIPEC, hyperthermic intraperitoneal chemotherapy.

(1,6-17,19-22,29): both the colon and lung directly adhere to diaphragm and the fistula forms between colon and lung through diaphragm; type II, CBF secondary to diaphragmatic hernia (8 cases) (2,3,17,18,23,24): the colon goes through diaphragm to form diaphragmatic hernia, directly adheres to lung tissue and forms fistula; type III, CBF secondary to sub diaphragmatic abscess or empyema (7 cases) (4,5,25-28,30): the colon and lung tissue fistula connect indirectly through the sub diaphragmatic or pleural abscess; type VI, CBF secondary to colon interposition (2 cases, *Figure 2*) (31,32).

For type I cases, the causes included Crohn's disease (6 cases), colonic malignancy (3 cases), postoperative intraperitoneal adhesion (4 cases), abdominal radiation (1 case), diaphragmatic mesh repair (1 case), tuberculosis (1 case) and pulmonary infection or abscess (4 cases, *Table 1*). For type II cases, traumatic (4 cases) and un-traumatic (4 cases) diaphragmatic hernias were the causes (*Table 1*). For type III cases, the causes included postoperative intraperitoneal adhesion (3 cases), Crohn's disease (2 case), HIPEC (1 case) and pyonephrosis (1 case, *Table 1*). For type IV, all 2 cases accepted colonic interposition (*Table 1*). There were 30 cases (2,4,6-10,12-14,16,17,19-21,23-32) with the left side fistula and 7 cases (1,3,5,11,15,18,22) with the right side fistula.

The clinical presentations of CBF

The clinical presentations of CBF included productive cough with (78.38%) or without (10.81%) foul smelling
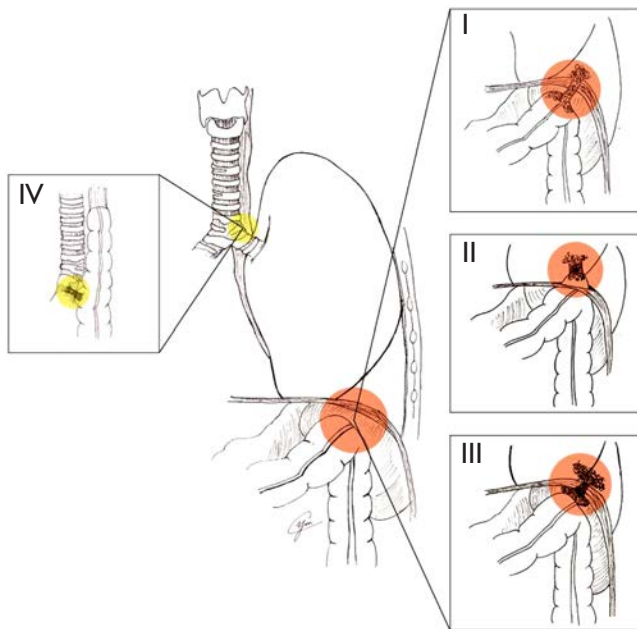
Figure 2 The classification of colobronchial fistula (CBF): type I, CBF secondary to the adhesion among colon, diaphragm and lung: both the colon and lung directly adhere to diaphragm and the fistula forms between colon and lung through diaphragm; type II, CBF secondary to diaphragmatic hernia: the colon goes through diaphragm to form diaphragmatic hernia, directly adheres to lung tissue and forms fistula; type III, CBF secondary to subdiaphragmatic abscess or empyema: the colon and lung tissue fistula connect indirectly through the subdiaphragmatic or pleural abscess; type VI, CBF secondary to colon interposition. CBF, colobronchial fistula.

sputum, weight loss (32.43%), fever (32.43%), chest pain (27.03%), dyspnoea (21.62%), hemoptysis (16.22%), dysphagia or diarrhoea (13.51%), hematemesis or melena (5.41%), and change of bowel habit (2.70%, *Table 2*).

The methods to confirm the diagnosis of CBF

The methods that finally confirmed the diagnosis of CBF included barium enema or water-soluble contrast enema study (67.57%), CT scan/with multiplanar reconstruction (16.22%), barium swallow (10.81%), flexible sigmoidoscopy or colonoscopy (2.70%), and postmortem examination (2.70%, *Table 3*).

The treatment and outcome of CBF

The treatment included etiological treatment, nutrition supporting treatment and surgery. Among 37 patients, 35 patients (94.59%) accepted the surgical interventions. Among these 35 patients, 33 patients accepted the resection of the fistula, the related colon with (14 cases) or without (19 cases) lung tissue, and repair of the diaphragm; 2 patients accepted colostomy because of poor condition. For the other 2 patients, 1 patient (7) refused consent for the operation and 1 patient (31) accepted esophageal stent implanting. The follow-up results can be got from 31 out of 37 patients (83.78%). 26 patients were discharged from the hospital with a good recovery, but 5 patients died in

Table 2 The clinical presentations of colobronchial fistula

Clinical presentations	N (%)	References
Cough		
With foul smelling sputum	29 (78.38)	(1-9,11,13,15-22,24-30), our case
Without foul smelling sputum	4 (10.81)	(12,14,24,31)
Weight loss	12 (32.43)	(1,6,7,10-13,19,22,25,30), our case
Fever	12 (32.43)	(1,2,4,5,10,12,13,16,23,24,27,28)
Chest pain	10 (27.03)	(1,8,12,13,17-19,24,28)
Dyspnoea	8 (21.62)	(6,10,18,19,22,23,29), our case
Hemoptysis	6 (16.22)	(17,20,21)
Dysphagia or diarrhoea	5 (13.51)	(5,7,9,10,31)
Hematemesis or melena	2 (5.41)	(12,32)
Change of bowel habit	1 (2.70)	(30)

N, number of patients.

Table 3 The methods to confirm the diagnosis of colobronchial fistula

The methods to confirm the diagnosis	N (%)	References
Barium enema or water-soluble contrast enema study	25 (67.57)	(5,7-12,16,17,19-30)
CT scan/with multiplanar reconstruction	6 (16.22)	(1,4,6,14,18), our case
Barium swallow	4 (10.81)	(2,3,31,32)
Flexible sigmoidoscopy or colonoscopy	1 (2.70)	(15)
Postmortem examination	1 (2.70)	(13)

N, number of patients; CT, computed tomography.

1 month after treatment. The reasons of death include uncontrolled infection (5,23,30), carcinoma (13) and pulmonary embolus (24).

Discussion

Owning to the complex etiology and the complicated clinical presentations of CBF, this disease is not fully understood and easily delayed in clinic. Therefore, it is necessary to carefully review and summary these 37 cases which have been reported in our institute and in literature for further understanding this disease.

The causes of CBF are complicated. Anything which may induce the direct or indirect connection between colon and lung tissue may result in CBF. In order to easily understand the pathogeneses of CBF, we developed a classification system based on the anatomical location and causes of fistula (*Figure 2*). For type I cases, Crohn's diseases, pulmonary infection or abscess, and iatrogenic intraperitoneal adhesions are the main reasons. The other reasons include colonic cancer invasion to diaphragma and pulmonary tuberculosis induced adhesion. For type II cases, diaphragm hernia increases the incidence of this fistula formation between colon and bronchus. For type III cases, the spontaneous rupture of a subphrenic abscess which goes into adjacent colon, penetrates the diaphragm into the pleural cavity and further into the adherent lung or vice versa, may be the cause. For type IV, it should be consider a complication of colonic interposition. It is worth noting that much more attention should be paid to patients with a history of Crohn's diseases and abdominal surgical or radiological interventions. Probably, Crohn's diseases and abdominal iatrogenic interventions may increase the incidence of abdominal organ adhesions or abscess formation. Although the left side CBF is more commonly reported because of the existence of liver in the right upper quadrant of the abdomen, there are still 18.92% patients with right side CBF. The abdominal surgical intervention in the right side such as hepatic resection, right nephrectomy and right diaphragmatic surgery may increase the risk of right CBF.

The clinical presentations of CBF are various because they refer to both the respiratory system and digestive system (*Table 2*). But for CBF, the respiratory symptoms such as cough, chest pain, dyspnoea and hemoptysis, are much more common than digestive symptoms such as diarrhoea, hematemesis and change of bowel habit. The most characteristic symptom for CBF is productive cough with foul smelling sputum, which should be paid much more attention and raise the suspicion for this disease.

In clinic, it usually takes a long time to confirm the diagnosis of CBF because of the complicated pathogenesis and various clinical presentations. Besides routine laboratory tests and chest radiography, some specific examinations should be performed to confirm the existence of fistula (*Table 3*). The barium enema or water-soluble contrast enema study has a unique role in diagnosis of CBF. Most of the patients can be detected the existence of fistula by using barium enema or water-soluble contrast enema study. Considering the potential risk of barium or water soluble contrast spillage into the fistulous tract or the lungs, which could be a source of infection and may not be easily removed, a CT scan with multiplanar reconstruction has been widely used to visualize the fistula recently. By using CT scan with multiplanar reconstruction instead of barium enema, 16.22% cases had been confirmed. The other valuable diagnostic methods include flexible colonoscopy and postmortem examinations. A combination of radiological and endoscopic investigations is more helpful to obtain a clear and confirmed diagnosis for CBF. Sputum culture with intestinal flora positive, such as *Escherichia coli*, is helpful for the suspicion of CBF (14).

The treatment of CBF is not easy. Owning to the infection and fasting, the patients are usually in very poor condition. Therefore, the antibiotic treatment and total parenteral nutrition are essential, which may control the infection and provide a relative better condition for further surgical treatment. At the same time, Specific treatment aiming to different causes should be performed. For example, infliximab has been successfully used to treat a Crohn's disease induced CBF, which totally controlled the progress of Crohn's disease, resulted in dramatic clinical improvement and simplified surgical management (1).

Surgery may be the only way to cure the CBF. The basic surgical procedures include the resection of fistula, the related colon and the lung tissue. If the CBF is nonmalignant, the surgeon should try to resect the lung and colon as little as possible. Our study implied that 57.6% (19/33) patients did not need the lung tissue resection. If the CBF is malignant, the surgeon should try to remove the tumor, dissect the lymph nodes, resect the fistula, and reconstruct the respiratory system and digestive tract at the same time. But it is very challengeable for the surgeon. Even though medicine has been developed quickly, the mortality of CBF isn't reduced recently. There were 3 (13,24,30) out of 23 patients died of CBF from 1960 to 2000, and 2 (5,23) out of 14 patients died of CBF from 2000 to 2012, which means much more efforts should be made to improve the treatment of CBF in future.

There is a limitation in this study. Owning to the low morbidity of this disease, most of the data in this study comes from the literature. Some important information may be not reported because the authors may concentrate on different aspect in their own publications. But, through this overall study, a panoramic view of CBF can be provided, which is helpful for the thoracic and general surgeons to understand and treat this disease.

In conclusion, CBF is a rare disease with complicated clinical presentations. Productive cough with foul smelling sputum is the most important symptom. Radiological investigations such as barium enema and/or CT scan with multiplanar reconstruction, combined with endoscopic investigations, are valuable for the diagnosis of this disease. Surgical treatment based on the etiological treatments may be the best choice for the patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The review of the patient's information was approved by the review board of Tangdu Hospital.

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The anesthesia of trachea and bronchus surgery

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Abstract: The trachea and bronchus surgery is generally performed due to stenosis, traumatic injury, foreign body and tumors. Preoperative evaluation and anesthesia management are very important issues because of higher mortality and morbidity rates. Patients may be asymptomatic, but airway difficulties, hypoxia, stridor, cough, hemoptysis are common conditions in these patient population. The collaboration between the surgeon and the anesthesiologist is very substantial and necessary. Anesthetic techniques include various applications such as one lung ventilation, fiberoptic intubation, jet ventilation, and apneic oxygenation, general anesthesia with or without neuromuscular blockade. In this review, anesthesia management of the trachea and bronchus surgery is evaluated in the light of new knowledge.

Keywords: Anesthesia; trachea; bronchus; surgery

Introduction

The trachea, main stem bronchi, bronchus intermedius and lobar bronchus make up the central airway. Disorders of central airway lead to disturbing symptoms such as cough, dyspnea, stridor, tachypnea, and hemoptysis (1-3). The trachea and bronchus surgery are mainly applied to stenosis, traumatic injury and tumors (4). Surgical approaches are one treatment option for central airway obstruction and other disorders. These approaches include complex interventions requiring one lung ventilation or cardiopulmonary bypass (CPB) as well as non-complex interventions such as dilatation (5). Anesthesia management for patients undergoing trachea and bronchus surgery is important in terms of protection of airway integrity and anesthesia maintenance. Therefore, the aim of this review is to share recent developments regarding anesthesia for tracheal and bronchus surgeries.

Anatomy of the trachea and bronchus

The trachea is a semiflexible tube extending from the sixth through the seventh cervical vertebrae to the fourth through fifth thoracic vertebrae. It is 10 to 14 cm in length with diameter of 1 to 2.7 cm. The trachea consists of two portions: the extrathoracic trachea is above the suprasternal notch, and it is 4 to 5 cm in length. The intrathoracic trachea is below the suprasternal notch, and it is 6–9 cm in length.

The trachea divides into two parts at the level of the fifth through sixth thoracic vertebrae, right and left main stem bronchus. The right main stem bronchus is wider and shorter than the left main stem bronchus. It is also separated from the trachea by steeper angle (6-9).

Tracheal stenosis

The etiology of tracheal stenosis involves many factors. Tracheal stenosis most commonly occurs post-intubation and post-tracheostomy, and incidence ranges from 10% to 22% (7). Congenital diseases (tracheomalacia, webs, vascular rings), chronic inflammatory diseases (sarcoidosis, amyloidosis), infectious diseases (tuberculosis,

rhinoscleroma, papillomas), collagen vascular diseases (Wegener's granulomatosis, lupus), malign tumors, and foreign body aspiration are other causes (7,8). Malign tumors include primary tracheal tumor (squamous cell carcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma), metastatic tumor and masses of adjacent organs (thyroid, larynx, lung, esophagus and mediastinal masses) (8). Most of these reasons lead to intraluminal obstruction. The tracheal mucosa has been infiltrated by benign or malign tissues. These formations within the lumen will cause a blockage later. However, extraluminal obstruction of the trachea occurs as a result of extrinsic compression or submucosal infiltration of the mass. Unlike intraluminal obstruction, the mucosa is intact. Distinct from these obstructions is dynamic airway collapse that occurs because of weakness of the posterior tracheal membrane. The place of obstruction is important in terms of the surgical approach and anesthetic management. Endoscopic interventions, such as mechanical debulking, microdebrider, cryocanalization, electrocautery, and tracheal resection are surgical methods applied to the intraluminal obstruction. The endoscopic procedures are applied in conjunction with rigid bronchoscopy. Surgical approaches for extraluminal obstruction include the excision of the mass, causing compression and endoscopic interventions (e.g., stent placement). Similarly, it may also apply endoscopic intervention for dynamic airway collapse (9).

Preoperative assessment

Primarily, patients with tracheal stenosis are evaluated with regard to medical history and general physical examination. The airway and pulmonary systems, in particular, should be assessed in detail, because they usually reveal nonspecific respiratory symptoms that include stridor, hoarseness, wheezing, progressive dyspnea, and reduced exercise tolerance (10,11). These symptoms occur 8 mm below or at a 50% reduction in the internal diameter of the trachea. Furthermore, if the internal diameter is 5–6 mm, inspiratory stridor is seen at rest. It is also important to evaluate the patient's respiratory function in the supine position. If the patient's breathing pattern is disrupted in the supine position, the anesthesia should be initiated in the appropriate position for the patient (8). Additionally, the patient should be questioned regarding the use of steroid and previous radiation therapy. Steroids may be associated with airway anastomotic dehiscence and delay in

wound healing. Radiotherapy to the neck region can cause restricted neck movement (10).

Other investigated parameters are pulmonary function tests, arterial blood gas analysis, posteroanterior and lateral chest radiography, computerized tomography (CT), magnetic resonance imaging, and flexible bronchoscopy (12,13). Pulmonary function tests, particularly flow-volume loops, may provide information about the degree of the tracheal stenosis, but it is not specific and sensitive for diagnosis for diagnosis. Furthermore, airway crisis may be triggered during these tests. Reduced forced expiratory volume in one second (FEV1) can be interpreted in favor of obstruction (13,14). Variable intrathoracic obstructions indicate flattening in the expiratory limb of the flow-volume loop. Extrathoracic obstructions indicate flattening in the inspiratory limb of the flow-volume loop. However, fixed intra- and extrathoracic obstructions show flattening in the inspiratory and expiratory limbs (2,7). A baseline value of arterial blood gas analysis may be a guide for postoperative management.

Monitoring

Standard monitoring includes electrocardiography (ECG), non-invasive blood pressure, pulse oximetry, and end-tidal carbon dioxide ($ETCO_2$) measurement (11). However, invasive monitoring may be required for patients undergoing tracheal resection. Arterial catheterization is used to evaluate hemodynamic and arterial blood gas changes, and the left radial artery is frequently preferred for catheterization (8). For vascular access, a peripheral intravenous (IV) (18–20 gauge) or central venous catheter may be used. Peripheral access will be sufficient for fluid management. However, the use of a central venous catheter may be necessary with inotropic drugs and in patients with cardiac problems. In such a case, the femoral or subclavian vein is most often used for catheterization (8,14).

Anesthesia management in rigid bronchoscopy

Rigid bronchoscopy is the initial phase of surgical approaches for tracheal lesions, and it is difficult to tolerate by an awake patient. Therefore, for these patients, general anesthesia is recommended in the operating room. Premedication should be avoided in patients with severe stenosis. The use of antisialogogues is not routine to reduce secretions. Furthermore, these drugs can increase the degree of stenosis by creating a mucous plug (11,12).

The surgeon should be available when induction begins, and pediatric- and adult-sized rigid bronchoscopes must be present in the operating room. The patient is placed on the operating table in the supine position. The roll is placed below the shoulder, and the neck should be hyperextended (15). After preoxygenation, IV (e.g., propofol, thiopental) and inhalation agents are used for anesthesia induction. In this instance, anesthetic agents are administered by titration, and after adequate anesthesia depth is achieved, local anesthetics such as lidocaine, may be administered into the pharynx and trachea to decrease the airway's response to instrumentation during rigid bronchoscopy (12). There are two important issues regarding ventilation: spontaneous ventilation during induction generates negative inspiratory intratracheal pressure, and it increases stenosis. Positive pressure ventilation creates positive intratracheal pressure. Therefore, positive pressure ventilation is preferable in patients with extrathoracic stenosis (e.g., tracheomalacia), whereas spontaneous ventilation may be applied in intrathoracic stenosis (14,16). After providing airway security, a dose-dependent, fast-acting non-depolarizing, or depolarizing muscle relaxant may be used as a neuromuscular blocking agent. Recent reviews reported that, despite the side effects of succinylcholine, it is superior to rocuronium in terms of intubation (17,18).

Total intravenous anesthesia (TIVA) or volatile agents can be used for anesthesia maintenance. Options for TIVA are propofol, remifentanil, ketamine, and dexmedetomidine. These drugs are implemented through target controlled infusion systems. TIVA is different from volatile agents used during ventilation. In the endoscopic interventions, several ventilation techniques are needed, and apneic periods or air leaks from the bronchoscope may occur during the procedures (19). At this stage, volatile anesthetics constitute a problem because of distribution, and maintenance of anesthesia is interrupted. However, TIVA does not cause such a problem because of continuing anesthesia (20). If volatile anesthetics are preferred, additional IV anesthetics should be applied during the apneic periods (11). Sevoflurane can be selected as volatile anesthetic because its effects are less irritating than those of other volatile anesthetics (21). During ventilation, a mixture of nitrous oxide (N_2O)-oxygen (O_2) or oxygen-air can be used. Further, a bispectral index (BIS) may be employed to assess the depth of anesthesia in patients receiving TIVA (20).

It should be noted that tracheobronchial surgery requires collaboration between the surgeon and the anesthesiologist. Such cooperation is especially important at the ventilation

stage. Several ventilation techniques can be applied during rigid bronchoscopy. These include apneic oxygenation, spontaneous ventilation, controlled ventilation, manual jet ventilation (low-frequency jet ventilation), and high-frequency jet ventilation (HFJV). Manual jet ventilation is the most commonly used ventilation technique during rigid bronchoscopy (19). HFJV (60–600 cycles/min) is provided by ventilators, and it diminishes airway pressures and the risk of barotrauma (14,22). Ventilation is performed with connection placed onto the bronchoscope.

If tracheal resection is planned after rigid bronchoscopy, the patients are intubated. If there is stenosis in the upper trachea, an appropriate-sized endotracheal tube (ETT) may remain at the level of the vocal cord, which results in an air leak. Therefore, a small ETT can be used, but it may hypercapnia. If there is stenosis in the mid-trachea, an ETT is advanced above the stenosis. Tracheostomy may, rarely, be necessary for a patent airway (11,23). However, upper tracheal resection may be also performed through laryngeal mask airway (LMA). But it has some disadvantages: the patients who critical airway stenosis may be inadequate ventilation (10,24).

Anesthesia management in the tracheal and carinal resection

Premedication, drugs used in anesthesia management and position are similar with rigid bronchoscopy. For upper tracheal lesions, the trachea is explored through cervical incision (color incision, U-shaped) (23). The location of the incision is between the lower part of the cricoid cartilage and the sternal notch. Cervico-mediastinal incision is applied for middle tracheal lesions. For lower tracheal lesions, the surgical approach is median sternotomy or right thoracotomy (4,25).

During anesthesia induction, the ETTs must be prepared for intubation (11). For the correct placement of the ETT, fiberoptic bronchoscope (FOB) can be used (12). In the presence of upper tracheal lesion, ETT is placed in the trachea above the lesion. Surgical processing is initiated after sterilization of the surgical site following intubation. The trachea is exposed, and the first incision is applied at the distal end of the obstruction (26) (*Figure 1*). After confirming the ETT, it is withdrawn into the proximal trachea. Simultaneously, a sterile ETT is placed into the distal trachea by the surgeon (4) (*Figure 2*). This tube is connected to a sterile anesthetic circuit, across the surgical field. Ventilation is maintained by the anesthesiologist and
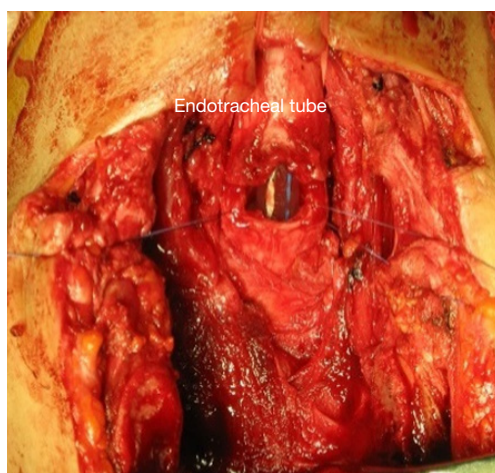
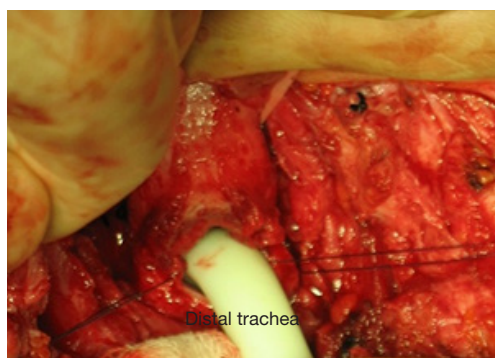**Figure 1** Endotracheal tube during tracheal incision.

Figure 2 Distal endotracheal tube.

confirmed by evaluating chest inflation, peripheral oxygen saturation, ETCO$_2$, and blood gas analysis (8,11). Resection of the tracheal lesion is completed with circumferential dissection, and anastomosis is then started. After surgery, patients are reintubated and ETT is removed from the distal trachea. The intubation tube is advanced to the bottom of the anastomosis (4,26) (*Figure 3*). Furthermore, retrograde intubation may be performed via the flexible catheter; therefore, contamination of the surgical field may be prevented (4,8). The anastomosis is tested in terms of air leak. Therefore, the patients should be ventilated with 20–30 cmH$_2$O pressure (11,15).

Ventilation may be provided through the ETT, jet ventilation catheter, tracheostomy cannula, LMA, and different ventilation strategies can be performed during tracheal resection (12). These strategies include manual jet ventilation and high-frequency ventilation (5,27). Manual
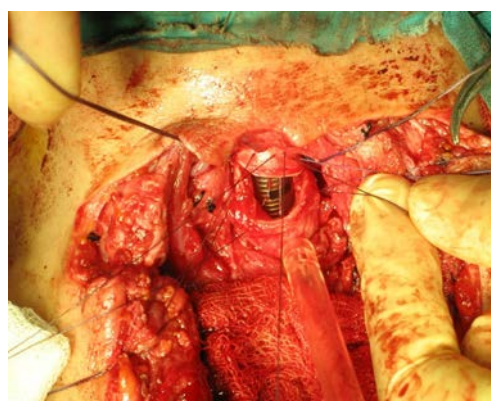

Figure 3 Endotracheal tube during anastomosis.

jet ventilation applies in various ways, such as ETT and catheter. This ventilation provides high tidal volume but, it carries the risk of hypercapnia (5). Small-bore ETT and catheter are used for high-frequency, and it can be used in three different modes: high-frequency positive pressure ventilation (HFPPV), high-frequency jet ventilation (HFJV), and high-frequency oscillation ventilation (HFOV). If diameter of the distal trachea is narrow and there is difficulty during the surgical procedure, HFPPV can be performed in these patients (27). HFOV is implemented most often for lung surgery, such as lobectomy and pneumonectomy. Advantages of high-frequency ventilation are as follows: good gas exchange, reduced ventilation/perfusion mismatch and atelectasis due to auto positive end-expiratory pressure, and minimal hemodynamic changes (5). LMA can be used in airway management of tracheal resection. Biro *et al*. reported that LMA is a safe approach for ventilation and surgical exposure in serious upper-tracheal stenosis (28).

Anesthesia management for distal trachea and carina obstructions is slightly different than that for upper tracheal lesions. The surgery approach for these obstructions is right posterolateral thoracotomy. Ventilation strategies during surgery involve one-lung ventilation (OLV), extracorporeal membrane oxygenation (ECMO), or CPB (5,29). Different approaches are used for OLV. After the ETT is pulled above the lesion during surgery procedure, the endobronchial blocker, ETT or single lumen endobronchial tube may be preferred for placement into the left mainstem bronchus (5,12,21). According to the airway devices used, low-frequency jet ventilation or low tidal volume ventilation are applied during resection (12,30). ECMO is another alternative strategy for gas exchange. It can be performed veno-venously or veno-arterially (29).

At the end of resection and reconstruction, ETT is placed above the anastomosis line, and ventilation is conventionally maintained (11).

If the patient's respiratory effort is adequate, extubation should be planned in the operating room. Prolonged intubation can disrupt the anastomosis line because of positive pressure ventilation and tracheal irritation (25). However, in the patients who underwent carinal resection and prolonged operation, postoperative mechanical ventilation may be required for respiratory support (8). Before extubation, neck flexion is supported with a suture between the chin and the manubrium sterni. The aim is to decrease anastomotic tension (15). In the extubation period, anesthesia preparations should be made for possible airway problems. Because emergent intubation and reintubation may be needed, intubation should be made through FOB (5,8).

Pain management

In patients with cervical incision, postoperative analgesia options may include systemic opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). Epidural analgesia, paravertebral and intercostal blocks, and systemic analgesia, such as opioids and NSAIDs, may be preferred for patients with thoracotomy (12,25,31,32).

Postoperative care

During the postoperative period, the patient's head should be kept elevated in a supine position to reduce swelling (5). Postoperative pulmonary care is important for these patients. Possible lung pathologies, such as pneumothorax and atelectasis, are evaluated by a posteroanterior chest radiograph. Also important is removal of tracheal secretions. For this reason, chest physiotherapy may be recommended (15). On the fifth through seventh postoperative days, anastomosis healing is assessed by FOB. After suture which used for neck flexion is cut, the patient's discharge from hospital is planned (25).

Complications

The literature reports average mortality rates of 3% and 2–20%, respectively, in tracheal and carinal resection (8,30). Postoperative complications can be seen in the early late period. Early complications involve respiratory distress and vocal cord paralysis. During surgery, the recurrent laryngeal nerve may be damaged. This situation may result in vocal cord paralysis after surgery, and may lead to hoarseness and dyspnea (8). Later complications can be anastomotic, such as granulation tissue, necrosis, and dehiscence as well as hemoptysis (8,30).

Tracheobronchial injuries (TBIs)

TBIs are rare, but may be fatal. Penetrating or blunt trauma to the chest or neck lead to TBIs. The reported incidence of TBIs is 0.5% to 2%. Injuries caused by blunt trauma are seen in the intrathoracic trachea and mainstem bronchus, whereas penetrating trauma affects the extrathoracic trachea. Symptoms occurring in airway injuries involve dyspnea, respiratory failure, hoarseness, and dysphonia. Subcutaneous emphysema, pneumothorax, and hemoptysis can be seen in patients with trauma. Chest radiography, neck and chest CT are required for diagnosis. FOB is the best method to assess the size and location of injury.

TBIs usually require multidisciplinary approach due to possible injuries to multiple organs. Airway management is extremely important in patients with TBIs. These patients may require immediate intubation because of respiratory failure and hemodynamic instability. At this stage, FOB guided endotracheal intubation would be a rational approach. In some cases, ventilation is accomplished through tracheostomy, and intubation is accomplished through an open neck wound and nasotracheal intubation (33).

Anesthesia management of these patients should be done in collaboration with the surgeon and the anesthesiologist. Airway management has been mentioned above. In addition, tube selection is an important detail. Double-lumen tube is not recommended for intubation. Long ETTs, single-lumen tubes, endobronchial blockers are options used for successful ventilation (33). Anesthesia maintenance and ventilation strategies are similar with tracheal stenosis (see trachea stenosis). Manual jet ventilation, HFJV, one lung ventilation and CPB can be performed according to the localization and size of tracheal injury (34,35).

Postoperative care involves closely respiratory and hemodynamic monitoring of patients (34).

Bronchus surgery

Bronchial surgery is one of the most commonly used procedures in thoracic surgery and is generally applied in instances of tumors, foreign bodies, and trauma. Endobronchial tumors and foreign bodies may lead to bronchial obstruction, severe dyspnea, and finally, collapse

of the affected lung. Preoperative evaluation of the patients is very important for bronchus surgery and is similar to tracheal surgery. Bronchoscopic techniques, including rigid bronchoscopy or flexible fiberoptic bronchoscopy, are used for laser therapy, foreign-body removal, and the placement or control of the lung isolation device.

Bronchus tumors

Bronchus tumors are generally seen in two forms: primer or recurrent lung cancer and metastases from other organ tumors (36). The most common symptoms are dyspnea, cough, and hemoptysis. Pneumonia, abscess, and recurrent infections can be observed and life-threatening stridor may occur in obstruction of the main bronchus. Distal tumors are often asymptomatic, and a diagnosis is usually established through routine radiological examination. The treatments include laser therapy, bronchial stent placement, photodynamic therapy, argon beam coagulation, radiotherapy, and surgical excision with or without bronchoscopy, and a combination of these techniques (36-38).

Laser therapy is one of the most commonly used treatments for bronchial tumors. However, if sufficient measures are not taken, serious risks may occur, such as corneal and retinal damage, airway fire, gas embolism, perforation of an organ or vessel, airway hemorrhage, pneumothorax, and tracheoesophageal fistula (39). During laser therapy, it is recommended that all operating room personnel (doctor, nurse, technicians, etc.) use special eyeglasses. The patient's eyes must be protected by closing the eyelids with tape and saline-soaked pads. Windows should be covered and warning signs should be placed outside the door.

Airway fire is rare but most feared complication associated with laser application. The use of special laser-resistant tracheal tubes and inflation of the ETT cuff with saline and a colored indicator are suggested for the prevention of the fire. The use of oil-base balm to increase the lubricity of the ETTs is dangerous because of the combustible nature of these substances. Minimal oxygen concentration (inspired oxygen concentration <40%) allows for sufficient oxygenation of the patients to be used to avoid potential airway damage (40-42). A mixture of oxygen-air is more suitable than an oxygen-nitrogen mixture, which is highly combustible (43). In the event of an airway fire, laser therapy and ventilation are terminated, the oxygen source is removed, and the patient is extubated. The patient is then ventilated with a face mask, and airway is evaluated

for possible damage with rigid or flexible bronchoscopy. If damage is suspected, the patients are reintubated, tracheotomy may be required, and steroids may be used to decrease mucosal edema. In addition, inhale bronchodilators may help to reduce possible bronchospasm.

Laser therapy is performed with fiberoptic or rigid bronchoscopy. Several anesthetic approaches—awake or general anesthesia and nasal or oral intubation—are applied for flexible bronchoscopic intervention. In the presence central airway obstruction, the first choice may be fiberoptic bronchoscopy awake or step-by-step general anesthesia protecting spontaneous ventilation (44). Premedication with sedative drugs is not recommended in patients with airway obstruction but antisialagogues and anticholinergic drugs may be used. Awake technique can be performed with topical anesthesia via nebulizer, aerosol, or local anesthetics-soaked pads, local anesthesia via laryngeal or glossopharyngeal nerve blocks or direct application of local anesthetic as spray via bronchoscope (45). The use of an ETT with a large internal diameter facilitates the fiberoptic placement and adequate ventilation of the patient. LMA can be used for the fiberoptic technique, especially in patients with difficult airways, and LMA also leads to lower airway resistance during bronchoscopy (46,47). IV or inhalation agents are preferred for anesthesia induction and maintaince. Propofol helps to suppress the laryngeal reflex and provides better clinical conditions than the other IV agents (48,49). If paralysis is required, short-acting neuromuscular blocking agents should be preferred because partial airway obstruction may convert to complete obstruction (16,50). These interventions have minimal postoperative pain and only short-acting opioids are recommended.

Rigid bronchoscopy, the other alternative technique for laser therapy, provides better visibility and airway control because of ventilating instrumentation and a minimal fire hazard (50). In addition, general anesthesia with neuromuscular blockade, spontaneous ventilation with topical anesthesia or nerve blocks, apneic oxygenation, and jet ventilation are applicable techniques for rigid bronchoscopy (51,52). Any movement of the patient during bronchoscopy may result in serious injury, but the use of a neuromuscular blocker may be dangerous in patients with partial airway obstruction. Succinylcholine is a suitable neuromuscular blocker agent because of its short-acting properties. Nondepolarizing agents may be preferred for prolong interventions. During rigid bronchoscopy, the bronchoscopist is exposed to the anesthetic gases, and

higher $PaCO_2$ values may be observed with positive pressure ventilation due to interruption of the ventilation (50). TIVA allows for the provision of adequate anesthesia without interruption, and this anesthetic regimen also prevents the contamination of the operating room with anesthetic gases. Several other complications of rigid bronchoscopy include soft-tissue injury (mouth, lips, tongue etc.), tooth damage, sore throat, airway perforation, hemorrhage, airway edema, and laryngospasm.

The most common monitorization method for bronchoscopy (flexible or rigid) is pulse oxymetry because desaturation is a common and important condition in this intervention. End-tidal CO_2 values are not reliable because the patient's airway is open to the atmosphere. In the prolong process, arterial blood gas analysis may be beneficial. At the end of the bronchoscopy, the patients may be extubated and ventilated via a face mask. However, the patients with respiratory failure are again intubated after the procedure, and corticosteroids (methylprednisolone or dexamethasone) and inhaled epinephrine may be used in edematous airway situations. When respiratory function improves, the patients are extubated.

Bronchial stents are often used in bronchial obstruction due to bronchial tumors and stricture. Deep IV anesthesia with flexible bronchoscopy or general anesthesia with neuromuscular blockage can be preferred to placement of stents. This procedure is performed for both extrinsic compression and intraluminal stenosis in adult and pediatric patients without pain (53,54).

Photodynamic therapy can be performed under general anesthesia or topical anesthesia plus IV anesthesia. There is no risk of airway fire, and the patients may be ventilated with 100% oxygen if required.

Massive hemoptysis or bleeding due to bronchial tumors is a feared clinical condition. The main goal of anesthesia includes volume resuscitation, the separation of bleeding lungs, the protection of normal lungs, and providing sufficient oxygenation. In addition to standard monitoring (heart rate, non-invasive blood, and pulse oxymetry), invasive arterial catheterization and central venous catheterization are recommended. Large diameter IV catheters provide rapid fluid administration. Before anesthesia induction and intubation, the patient should be bleeding lung in a dependent position. This position prevents contamination of the healthy lung. Rapid and safe airway management must be provided in these patients. Fiberoptic awake intubation may be used, although visualization is difficult because of bleeding. Single-lumen endotracheal intubation followed

by endobronchial blocker, main bronchial intubation of unaffected lung with fiberoptic bronchoscopy, or double-lumen intubation may be used to separate of the lungs.

Bronchus foreign bodies

Bronchial foreign body aspiration is less common in adults than in children. It is generally seen in elderly male patients with Alzheimer's disease, psychiatric illness, or head trauma (55,56). The clinical symptoms include cough, dyspnea, wheezing, shock, hemoptysis, cardiorespiratory arrest, but the majority of patients may be asymptomatic. Early identification and intervention are crucial because it may cause life-threating complete or incomplete airway obstruction (56). Finally, respiratory distress, pneumothorax, asphyxia, lung abscess, pneumonia, asthma, bronchiectasis, and atelectasis may occur as complications (57). Bronchopleural and bronchopleural cutaneous fistulas and subcutaneous emphysema are possible rare complications because of foreign body aspiration (58,59). The definitive diagnosis includes chest X-ray imaging and CT (60). In chronic aspiration history, granulation tissue may occur around the foreign body. Rigid or flexible bronchoscopy plays a role both diagnosis and removal of the foreign body. Emergency tracheostomy may be required in the case of complete bilateral occlusion (61). If bronchoscopy fails, open thoracotomy may be used for successful removal. The patients are at risk in emergency cases for full stomach, and a large-bore gastric tube must be inserted before tracheostomy, but if the patient has respiratory and hemodynamic stability, the intervention may be delayed (62). An inhalation agent is generally used for anesthesia induction, but another option is controlled IV induction. Anesthesia maintenance is performed with IV or inhalation agents; neuromuscular blocking drugs may be used if necessary (48-50). During the removal of foreign body, falling back to tracheobronchial area is a life-threating condition (62). Therefore, adequate depth of anesthesia must be provided before removal of the body. If oxygenation and ventilation are impossible, ECMO may be a life-saving method (63).

Bronchopleural fistula

Bronchopleural fistula is rare but life-threating complication of thoracic surgery (especially pneumonectomy and lobectomy) and is associated with a higher risk of mortality and morbidity. The most common causes are rupture of

pulmonary structure into the pleural space (lung abscess, bronchus, cyst, parenchymal tissue, bulla), bronchial destruction (carcinoma, inflammation), stump dehiscence after pulmonary resection, and erosion of the pulmonary artery or vascular suture line (64). Incorrect placement of the enteral feeding tube and esophageal stent migration are the other uncommon causes (65,66). Clinical observation is very important factor for diagnosis. After thoracic surgery, dyspnea, emphysema, purulent drainage, permanent air leak, and tracheal deviation should be suspected of bronchopleural fistula. Fewer and purulent sputum may be first symptoms after removal of the chest tube. A decrease of the fluid level and new air-fluid level are seen in the X-ray imaging. The diagnosis is confirmed with bronchoscopy, methylene blue injection, inhalation of xenon, scintigraphy with Tc-99m DTPA, and inhalation of O_2-N_2O mixture (67,68). In early postpneumonectomy patients, resuturation may be possible, but in delayed cases, open drainage or muscular flap may be necessary. If non-pneumonectomy bronchopleural fistula, treatment includes chest tube or surgical resection.

Anesthesia management may be complicated in these cases. The primary aims are the protection of healthy lung and providing oxygenation. Lung isolation devices (double-lumen ETTs or bronchial blockers) must be used for lung protection, especially with a larger fistula. Excessive higher pressure should be avoided because positive pressure ventilation may lead to tension pneumothorax. A chest tube should be placed before the induction of anesthesia as a measure for tension pneumothorax. Inadequate ventilation may occur because an air leak. Awake fiberoptic intubation with double-lumen or single-lumen ETTs, spontaneous ventilation until lung isolation, thoracic epidural anesthesia with IV sedation and HFJV may be used in patients with bronchopleural fistula (69).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Practical anesthetic considerations in patients undergoing tracheobronchial surgeries: a clinical review of current literature

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Abstract: Tracheobronchial surgeries require close cooperation and extensive communication between the anesthesia providers and the surgeons. Anesthetic management of tracheal and bronchial pathologies differ basically from regular upper airways management, due access to the patients airway is limited, mostly even practically impossible for the anesthesia providers. As a consequence, the surgeon overtakes responsibility for the airway access from the anesthesia provider in the variety of the cases. Preoperative recognition of a difficult airway, detailed planning and being aware of plan B and plan C are the elementary keys to success. Providers have to be aware, that preoperative airway assessment does not always correlate with the ease of oxygenation and ventilation. Therefore, various methods have been described in the literature and several authors have adopted unique ways to manage the airways in a successful manner. With the advancement of surgical techniques over the years, anesthetic management has also evolved tremendously to match the needs. The commonly encountered conditions requiring surgical interventions include post-intubation stenosis and foreign body aspiration. In this review we will discuss the most common pathologies of tracheobronchial lesions and specific anesthetic management considerations related to them.

Keywords: Anesthesia; tracheobronchial surgery

Introduction and background

Anesthesia for tracheobronchial surgeries has always been challenging. Despite the anesthetic and surgical refinements there are still no randomized trials comparing various methods of anesthetic management among these surgeries. Anesthesia for tracheobronchial surgeries is especially challenging, as anesthesia provider and surgeon share a common area of intervention. Therefore, close and effective communication between the anesthesia and surgery partners is essential. Over the years, numerous attempts have been made to improve the practice and several sophisticated technical approaches have been defined for various complex surgeries and diagnostic procedures. Advance planning, meticulous check-lists for anesthesia equipment, anticipation of possible complications, and good communication as well as coordination between the teams involved are the key components to design a successful anesthetic plan.

The most common pathologies that require surgical intervention of the airways are post-intubation complications (accounting for 75% of cases) (1), neoplasms of the lungs or the airways and congenital airway anomalies.

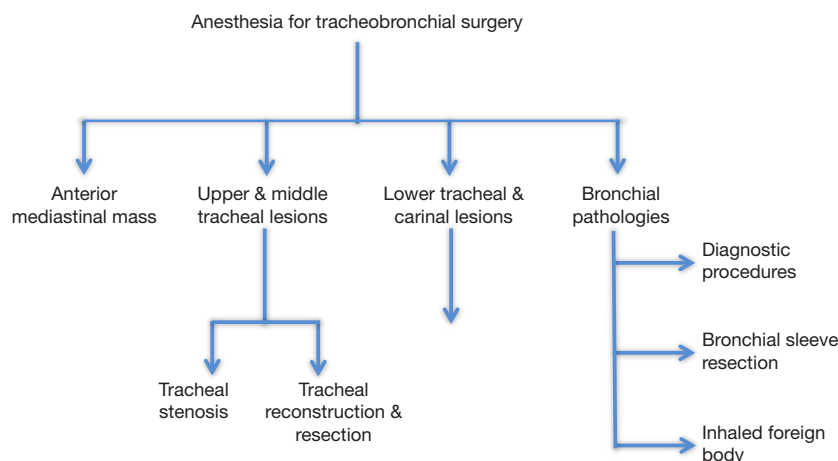The common patient characteristics presenting with

Figure 1 A short overview of tracheobronchial procedures.

tracheobronchial pathologies are either elderly with comorbid illness, compromised airways with tumors (post radiotherapy) or alternatively young patients with acute airway obstruction resulting from foreign body inhalation.

This review will provide an overview of safe anesthetic practices evolved over time for tracheobronchial surgeries and of the unique preparations required by anesthesia providers. Upper and lower tracheal surgeries require different approaches since algorithms pertaining to difficult airways do not apply once pathologies are distal to the vocal cords (2). The anticipated technical difficulties associated with these surgeries can be overcome by diligent pre-operative preparation.

This review will describe the anesthetic management of the various surgical procedures of the tracheobronchial airway, as described in *Figure 1*.

Tracheal anatomy and pathophysiology

The origin of the trachea is defined as the inferior aspect of the cricoid cartilage at the approximate level of the sixth or seventh cervical vertebra. Various factors like obesity, flexibility of neck, body habitus and kyphosis may change the position and mobility of the trachea. The trachea maintains its structure with the rigid support of 18 to 24 C-shaped cartilaginous rings while the posterior wall of the trachea is constructed of a membranous band that lacks cartilaginous support. The distal margin of the carina bifurcates into the left and right main bronchi at the approximate level of the fifth thoracic vertebra. The trachea is classically divided into:

(I) Extra-thoracic trachea, above the suprasternal notch, which comprises approximately a 1/3 of its total length;

(II) Intra-thoracic trachea, extending from the suprasternal notch till the carina, accounting for the remaining 2/3 of its total length.

Freitag and colleagues have classified the causes of tracheal stenosis as either structural or dynamic (3).

❖ Structural (or fixed, intraluminal) stenosis occurs due to all types of exophytic intraluminal malignant or benign tumors and granulation tissue; extrinsic compression; narrowing due to airway distortion, kinking, bending, or buckling; and shrinking or scarring (e.g., post-intubation stenosis).

❖ Dynamic (or functional) stenosis is caused by a triangular-shaped or tent-shaped airway, in which cartilage is damaged, or alternatively an inward bulging of the posterior membranous wall (4).

The neoplastic growth usually follows a circumferential pattern, but resection along the same pattern is usually avoided during the surgery (5). The trachea is well supplied by the internal thoracic, intercostal and bronchial arteries through its lateral wall and might be vulnerable to ischemia during surgery.

The normal negative intrapleural pressure helps in providing stenting effect to the trachea and this effect is lost when the spontaneous respiration gets abolished with the induction of anesthesia.

Respiratory symptoms such as exertional dyspnea usually become evident once the tracheal lumen narrows to half its original diameter (6). Inspiratory stridor at rest indicates

Table 1 Major etiologies for tracheobronchial pathologies necessitating surgical interventions

Insult	Etiologies
Post-intubation stenosis	Too large tube, overinflated cuff—transmural injury causes cicatricial healing
Post-tracheostomy	Persistent compression leads to ischemia, ulceration, perichondritis and chondritis, stomal stenosis
Injury	Inhalational injury, penetrating or blunt external trauma, Irradiation, burns, intubation-related arytenoid injury
Benign neoplasms	Respiratory papillomatosis, carcinoid tumor
Malignant neoplasm	Primary: adenoid cystic and squamous carcinoma. Secondary: thyroid carcinoma, metastatic carcinoma
Chronic inflammatory disease	Amyloidosis, sarcoidosis, relapsing polychondritis, Wegener's granulomatosis
Infectious	Mycobacterium tuberculosis
Reflux disease	Primary stenosis/restenosis
Miscellaneous	Saber sheath trachea, circular tracheal rings, tracheomalacia, vascular anomaly
Bronchial tumors	Adenoma, adenocarcinoma, squamous cell carcinoma, neuroendocrine, carcinoid
Foreign body aspiration	Altered mental status, trauma, dental procedures, advanced age, impaired cough reflex

severe reduction in tracheal diameter.

The major pathologies and their most common etiologies are detailed in *Table 1*. The most common indication for tracheal surgery is tracheal stenosis, with post-intubation stenosis being the most prevalent etiology. Prolonged compression of the tracheal mucosa by an overinflated cuff or an oversized endotracheal tube may cause obliteration of mucosal blood supply further leading to ischemia, ulceration, and the formation of granulation tissue and fibrosis causing contracture. As a clinical consequence, it is advisable to maintain cuff pressure below 30 mmHg (7).

General considerations in pre-operative assessment

Preoperative assessment of the airway does not always correlate with the ease of ventilation and, therefore, the practice of managing airways varies among experts. The location of the stenosis could be divided into three regions: upper third, middle third, and lower third of the trachea.

Detailed medical history and physical examination with special consideration to airways and pulmonary systems, recent respiratory tract infections, exercise tolerance, patients preferred positions without short of breath, amount of pulmonary secretions and previous endotracheal intubations as well as demand of oxygen during the day at several activities should be noted. Neck mobility examination prior to surgery is essential as it is reported to facilitate both intra-operative exposure and post-

operative healing (8). History of chronic steroid exposure and radiation therapy is important as it can interfere with wound healing and may cause wound dehiscence (9).

Clinical signs and symptoms remain the most important set of information for evaluating a patient for tracheal surgeries. Nevertheless, the gold standard for evaluation of stenosis is formal bronchoscopy (10). The severity of airflow resistance correlates to the 4th power of the tracheal radius, assuming laminar flow (resistance α radius^4, Poiseuille's Equation). The pattern of dyspnea (or stridor) can be helpful in localizing the site of stenosis. Stridor and cyanosis are late signs and usually indicate near-total obstruction. The positions that alleviate or worsen airway obstruction are of crucial importance for the anesthesia provider and may become lifesaving during unexpected anesthetic events. Radiologic imaging is useful adjunct in assessing airways. Stenosis quantification done by CT scans and bronchoscopy have almost comparable results (11-13).

Pulmonary function tests might be helpful in predicting the likelihood of post-operative ventilatory dependence in the setting of pulmonary dysfunction and in monitoring the progress of obstruction after treatment (14-16). The clinical relevance of flow volume loops is questionable. Although not considered as a good predictor during usual preoperative evaluation, they might aid in identification of the inspiratory and expiratory irregularities or cause (fixed or dynamic obstruction) of tracheal stenosis (17).

Fixed/intraluminal stenosis causes decrease in the flow and plateau parts of both the inspiratory and expiratory

Table 2 Different methods of ventilation for tracheobronchial interventions, relevant mechanism and main advantages

Ventilation mode	Mechanism	Advantages
Intermittent positive pressure ventilation (IPPV)	High intrathoracic pressure	Inhaled anesthetic can be delivered; controlled respiratory rate and preset tidal volumes, CO_2 elimination; better monitoring with $EtCO_2$
Jet ventilation	Supraglottic, glottis or subglottic, delivered via a narrow cannula attached to a laryngoscope or bronchoscope	Airway stays free for surgeon, allows oxygenation and reasonable ventilation with no tracheal instrumentation
Spontaneous ventilation	Negative intrapleural pressure helps stenting the airways	Better tolerated in intrathoracic lesions
ECMO/CPB	Veno-venous or veno-arterial	Usually a final rescue option

ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass.

limbs of the flow-volume loop, whereas extrathoracic obstruction usually only influences the flow in the inspiratory limb.

General intraoperative considerations

The overall anesthetic goal is to maintain a patent airway, allow maximal surgical exposure, and have the patient fully awake and cooperative at the end of surgery.

The therapeutic options available for tracheal pathologies are tracheal reconstruction, laser or electro-cautery excision, tracheal dilation and stenting. The method of ventilation depends on the level of lesions and degree of airway obstruction, as detailed in *Table 2*. Spontaneous ventilation is better tolerated in intrathoracic lesions (18). This allows the patient to maintain airway patency using muscle tone and respiratory efforts.

The apneic oxygenation as described by Patel under the name of THRIVE (19) may well play an important role in the future, where the inner lumen of the trachea remains open enough. This oxygenation technique needs proper validation in the context of tracheobronchial surgery.

Anesthesia management of anterior mediastinal masses (AMMs)

AMMs can be benign (thymoma, cyst, thyroid mass, cystic hygroma) or malignant (thyroid/thymic carcinoma, lymphoma).

These masses often encroach on and exert pressure effects on the middle mediastinum causing severe respiratory and cardiovascular compromise leading to death (20,21). Although mortality pertaining to surgery and anesthesia is considered low, AMMs can cause compressive symptoms that might be life threatening, further exacerbated by general anesthesia. Mortality directly related to AMMs is reported as higher in the pediatric age group, possibly due to the compressible nature of the cartilaginous airways (22,23). New imaging modalities have almost eradicated the use of general anesthesia for diagnostic purposes.

Pre-anesthetic assessment involves focused history with special attention to local symptoms related to the mass and its pressure effects on intrathoracic organs. Superior vena cava obstruction requires special attention. Severe symptomatic superior vena cava syndrome (usually manifested as facial and upper extremities edema) may require cardiopulmonary bypass or extracorporeal membrane oxygenation cannulation prior to induction and good venous access in the lower extremities (24).

CT imaging may provide vital information, including the site and severity of the mass effect as well as its relationship to the airway. General anesthesia causes reduction in functional residual capacity, relaxation of smooth muscles and loss of spontaneous diaphragmatic movements, all of which precipitate decrease in transpleural pressure gradient and, thereby, promote airway and vascular collapse under the AMM's pressure (25). Spontaneous ventilation exerts some protective stenting effect on the trachea, explaining why imaging done during full consciousness cannot predict airway or even vascular effects seen once the patient is exposed to general anesthesia, and more so to muscle relaxants (25).

Echocardiogram is mandatory for patients with suspected cardiovascular collapse. Flow volume loops used to be a part of routine pre-anesthesia evaluation as a predictor of "variable

intrathoracic airway obstruction" (25) but were shown to have a limited correlation with airway obstruction (26). Nevertheless, post-operative complications can be predicted to some extent by two preoperative factors: tracheal compression >50%, and peak expiratory flow <40% of predicted value (27). Preexisting endocrine abnormalities, prior exposure to chemo-radiation and associated paraneoplastic syndromes must also be considered in the setup of AMMs.

Patients with large AMMs that cross the midline require sternotomy, and, therefore, placement of high thoracic epidural prior to induction should be considered in order to alleviate post-operative pain. Induction in a stepwise manner coupled with strict hemodynamic monitoring to detect early signs of cardiovascular collapse and intermittent blood gas analyses are common practices. Optimal positioning is crucial during induction. Dyspnea in the supine position warrants an upright posture during induction.

This strategy is helpful in stabilizing the patient and may become lifesaving while seeking an alternative plan. Patients with high risk of cardiovascular collapse may be maintained on spontaneous ventilation and avoiding muscle relaxants until definitive airway is established. This can be achieved by the administration of inhalational agents or IV medications such as propofol, remifentanil, dexmedetomidine (28) and others. Judicious use of short acting muscle relaxants and assisted ventilation with the aim of providing positive pressure ventilation might alternatively be considered. Awake fiberoptic intubation may be necessary if imaging shows non-compressible tracheal lesions.

The following strategies should be considered in the event of catastrophic airway or vascular collapse during anesthesia:

(I) Posture change—optimal posture determined by the preoperative evaluation;
(II) Ventilation via a rigid bronchoscope;
(III) Lightening the plane of anesthesia and awakening the patient;
(IV) Emergent sternotomy and elevation of the mass.

Confirmation of dynamic airway compression using fiberoptic bronchoscopy may also be considered if the clinical situation allows.

To overcome severe cardiovascular compromise, the use of cardiopulmonary bypass might be indicated (29). It should be emphasized, though, that cardiopulmonary bypass is hardly ever feasible if adequate preparations were not done ahead of time. Therefore cardiopulmonary bypass should not merely be considered as "on standby", but rather cannulation should be performed, usually under local anesthesia. Tubing should be primed before induction of anesthesia, to be prepared for anticipated hemodynamic or respiratory collapse.

Emergency management of tracheal stenosis

No definitive management is defined for the treatment of stenosis. The most effective immediate solution for stenosis includes endoscopic intervention by rigid bronchoscope and simultaneous administration of steroids, oxygen, racemic adrenaline and diuretics to decrease edema surrounding the lesion and relieve obstruction.

Mechanical dilation by balloon dilators

This approach transiently improves oxygenation by relieving the obstruction.

Tracheal dilation and stenting

The tracheal stenosis primarily follows circumferential pattern of growth, therefore emergent airways techniques like tracheostomy, cricothyroidectomies, trans-tracheal ventilation would not be beneficial.

The primary aim of stenting is to provide symptomatic relief in the conditions where the lesion is obstructing and surgery is practically impossible to perform. Mediastinal masses causing central airway obstruction may also benefit with this intervention as stents serve as bridge to palliative treatment. Providing anesthesia to this population is more challenging as it requires increased attention to local and systemic effects of malignancies like superior vena cava syndrome, endocrine abnormalities, fibrosis from previous radiotherapies, cardiovascular compromise from chemotherapy (30). The important surgical steps involved in tracheal stenting are identification of lesion, guide wire placement, threading of balloon over the guide wire and dilation of stenosis.

Lesions present below the vocal cords rarely presents with difficult intubation because of tracheal pathologies per se. However, distal lesion acts as dynamic obstruction and interfere with expiratory flow leading to "air trapping" of distal segments. Allowing adequate expiratory time by keeping a threshold on inspiratory pressures below 30 cmH$_2$O is a good strategy (31).

Tracheal stent itself is a stimulus to cause airway obstruction. Coughing should be avoided as it may cause

total obstruction. At presentation, patients should receive supplemental humidified oxygen and maintain upright position, this simple maneuvers helps to avoid coughing.

Surgical approaches involve the use of endoscopic procedures. Maintenance of airways is crucial in both rigid and flexible bronchoscope procedures. The use of both rigid and flexible bronchoscope has been described in the literature and both approaches.

Rigid bronchoscope insertion is preferable and quicker to achieve as it has an advantage of secured airways with good surgical exposure (31). Total intravenous anesthesia involving the use of analgesics, hypnotics and anti-secretory agents is preferred as volatile anesthetic delivery cannot be guaranteed. There is always a risk of aspiration with the use of rigid bronchoscope, so patients with full stomach, hiatal hernias, morbid obesity should be weighed with risks and benefits. Mouth guard should be used to prevent injury. Rigid bronchoscope is inserted after complete neuromuscular blockade and instillation of intermittent jet ventilation via side port. The four basic ventilation methods are (32):

    (I)   Spontaneous ventilation with inhalational anesthetic along with topical anesthesia or nerve block;

    (II) Apneic oxygenation method (allows surgical intervention for 3 minutes or longer) with or without oxygen insufflation;

    (III) Intermittent positive pressure ventilation (IPPV) with bronchoscopic ventilation;

    (IV) Jet ventilation during total intravenous anesthesia.

The complications associated with rigid bronchoscope are: airway perforation, hypoxemia, hemorrhage, airway edema. In patients where there is risk of potential airway loss after the procedure it is always prudent to intubate a patient with smaller ETT after rigid bronchoscopy.

The use of local anesthesia and inhalational techniques precipitate coughing and should be avoided (31). The most crucial steps are placement of dilator and stents over the stenosis. Newer expandable stents allows more room for the manipulation and they open up when they are positioned well in the stenosed segment.

A flexible bronchoscope can be threaded through the endotracheal tube or the laryngeal mask airway (LMA) where a rigid bronchoscope cannot be negotiated. The ET can be placed under sedation and tip of tube should be placed just above the stenosis. This approach involves insertion of ventilatory conduits such as catheters through stenosed segment. Stent placement may be difficult if the

obstruction is distal and may complicate the surgical field by tissue laceration, bleeding, and perforation.

During surgeries requiring the use of Nd:YAG (neodymium-doped yttrium aluminium garnet) laser, the inspired oxygen should be kept as low as possible (usually oxygen should not exceed 30%) to prevent airways fires.

Tracheal reconstruction and resection

Advance preparation is the key for successful management. Various size endotracheal tubes (cuffed and un-cuffed), microlaryngeal tubes, emergency cricothyroidotomies kits should be ready in the cart. Standard ASA monitors are used and further requirements depends on case to case basis and coexisting comorbidities. Wide bore IV cannula in bilateral upper limb is needed as upper extremities are usually tucked in and are inaccessible for the anesthesia provider during ongoing surgery. Ability to perform bronchoscopy and jet ventilation instillation should be handy in "cannot intubate" conditions (33). Blood pressure monitoring is usually done by left radial artery catheterization and pulse oximetry on the other side. Since the innominate artery is close to the trachea, compression of the trachea and subsequently the artery may cause conflicting readings. Identification of brachiocephalic compression is essential as confusion about actual hypotensive state and compression of brachiocephalic vein can be distinguished.

Initially the patient is placed in extended neck position to enable enough space for surgical manipulation and later on changed to neutral position to exert minimal tension on the anastomotic segment of trachea.

Maintaining adequate oxygenation and ventilations is necessary during all surgical partial sections. The optimal ventilatory approach is defined by the location of lesion in the trachea.

Prolonged and adequate pre-oxygenation during obtained spontaneous breathing and carefully titrated induction of anesthesia is obligatory indicated. Assistance to generate adequate tidal volumes is sometimes indicated during pre-oxygenation and should be performed as carefully and as convenient as possible for the patient.

Rigid bronchoscopic evaluation just after induction is sometimes necessary to look for exact location of the lesion to be resected, evidence of tracheomalacia and vocal cord mobility (34).

Jet ventilation via bronchoscope allows surgeon to reduce tissue load by serial dilation and restore the diameter of

trachea which is followed by tracheal intubation. The potential side complication is barotrauma and hypercarbia (32). Total intravenous anesthesia is an acceptable approach with intermediate acting muscle relaxant. Judicious use of small titrated doses of opioids is advocated keeping in mind the goal of extubation after surgery and in the same time provide adequate analgesia.

The distal tracheal intubation technique is done when upper and middle trachea surgery is planned. The ETT is pulled back and the care must be taken not to puncture the cuff when the incision is made by the surgeon. The distal segment is intubated with another ETT inserted by surgeon in sterile technique and confirmed by $EtCO_2$. Care must be taken to reduce the use of inhalational anesthesia as large amount of leak is expected during "open airway portion" of procedure to avoid anesthetic pollution. A laryngeal mask can also be used before the trachea is opened. Gas exchange during this time is performed in principle by one of these techniques: (I) jet ventilation; (II) IPPV and distal segment tracheal intubation; (III) manual ventilation; (IV) extracorporeal membrane oxygenation or cardiopulmonary bypass, which is performed in only high-specialized clinics. Anesthesia is primarily maintained by intravenous method during this phase.

Once the anastomosis is done and is ready to close, the upper trachea is again intubated with a separate ET in retrograde fashion. The cuff is positioned under fiberoptic visualization in such a way that it is distal to the sutures or site of lesion. Before complete closure, the surgical site should carefully examined to detect any bleeding or leakage.

A rapid test can be to check any leak in the tracheal anastomosis by deflating the cuff applying 30 cm of water pressure to the breathing circuit and spilling saline over the suture site. Look for bubbles as an evidence of air leak. Guardian sutures are placed to prevent excessive hyper extension of neck. Use of anti-emetic at this point would be helpful in reducing nausea. After emergence the patient neck should be in fully flexed position and positioned in semi sitting posture and ETT is removed under fibroptic visualization when the patient is fully awake. Supplemental oxygen should be given.

Emergence from anesthesia is the most critical step. Smooth extubation and prevention from coughing and even extensive patients movement is strictly indicated.

Coughing and pressure effects of ETT on the reconstructed segment have serious implications like anastomotic failure. Placing the patient in head up and neck flexed position with the help of guardian suture (suture between skin of mandible and chest) helps to improve ventilation. Assessment of recurrent laryngeal nerve is essential after surgery.

Lower tracheal and carinal resections may be more conveniently approached by right thoracotomy. Arterial blood pressure monitoring is essential for all thoracotomies as it involves release of the right hilar ligament which can cause compression of the cardiopulmonary system and decreased perfusion pressure. The anesthetic management is similar to upper tracheal lesions except the fact that emergency surgical access to the airway is not possible. A variety of airway devices can be used in an attempt to pass the low obstruction, e.g., long single lumen tubes, bronchial blockers and jet ventilation (35). Long lasting and/or technically extensively challenging tracheal reconstructions can be done on extracorporeal membrane oxygenation as it ensures stable hemodynamics and oxygen supply (36), but again is limited to highly specialized clinics..

Endobronchial tubes placed under fiberoptic guidance are preferred to double lumen tubes as the latter are too bulky to facilitate surgical procedure. Endobronchial jet catheters may be placed via an ETT and if necessary, differential lung ventilation can be achieved using two catheters.

Single lung ventilation is usually needed in order to provide optimal surgical exposure. All patients undergoing single lung ventilation usually have a variable level of shunt. Independent lung ventilation can be utilized in cases of continuous desaturation, but might interfere with the surgical procedure. Other options include:

(I)   Deflating the cuff of endobronchial tube and blocking the nose and mouth while delivering large tidal volumes;

(II) Placing an additional endotracheal tube high up in trachea;

(III) A laryngeal mask can be placed after the endotracheal tube is in place and provide a seal to deliver sufficient tidal volumes;

(IV) Jet catheter can also be placed in the deflated lung.

Postoperative pain management is essential as the thoracotomy itself is considered a large and painful intervention (37). Thoracic epidural catheters are commonly used for post-operative pain control. Judicious use of systemic opioid agents is also possible, as long as respiratory depression is avoided. Prolonged surgeries requiring lower tracheal or carinal resection usually require post op ventilation for up to 24 hours.

Patients with previous history of lower tracheal or carinal surgeries who are undergoing other surgeries should usually

be carefully intubated under fiberoptic guidance, to avoid tissue damage or malpositioning due to altered anatomy.

Anesthesia for bronchial surgeries and procedures

The advancement of diagnostic and therapeutic bronchial procedures in recent years with more sophisticated navigation capabilities, such as endobronchial ultrasound guided fine-needle-aspiration and electro-magnetic navigation bronchoscopy, has necessitated the development of modern anesthesia management tools as well (33). These procedures are usually performed in remote locations by their mere definition, with their inherent anesthetic challenges of scarce rescue and emergency resources. Another serious concern is the usually impaired physical status of the patients. These patients may suffer from severe co-morbidities including for example bronchial tumors or chronic airway infections with limited pulmonary function.

Another subset of patients that are indicated for urgent bronchoscopy are young children and vulnerable adults who present to emergency room with suspected foreign body aspiration. The presenting symptoms can be stridor, dyspnea, dysphagia, hemoptysis or signs of hypoxemia. Imaging may reveal collapse or consolidation distal to the foreign body or emphysematous distention.

Premedication in the form of anxiolytics should be carefully considered in very anxious patients, and might be especially important in the pediatric population. The need for monitoring after anxiolytics should be assessed and planned accordingly. Supplemental oxygen and anti-sialagogues are routinely administered.

The different anesthetic alternatives for bronchoscopic interventions are: (I) general anesthesia; (II) conscious sedation; (III) monitored anesthesia care.

Preferred techniques for most of the prolonged bronchial procedures are general anesthesia with total intravenous anesthesia. Intermediate acting muscle relaxants are indicated as the surgery requires introduction of a bronchoscope through the vocal cords. Muscle relaxants will also prevent excessive coughing and laryngospasm.

Anesthesia for bronchial sleeve resection

This procedure involves removal of a circular sleeve in the main bronchus leaving lung parenchyma intact, and is considered for patients with insufficient cardiopulmonary reserve indicated for pneumonectomies. As previously mentioned, pulmonary function tests might predict post-operative ventilatory dependence (14). Double lumen tubes or bronchial blockers are the common devices used for lung isolation. The "Open lung" approach warrants the need for thoracic epidural for post-operative pain management. If a video-assisted thoracoscopic surgery is planned, paravertebral block can be considered (38).

Anesthesia for Inhaled foreign body

This is the leading cause of accidental death in the population younger than 4 years of age (39,40). Almost 80% of foreign bodies are made of organic material. Classic symptoms include dyspnea, stridor, aphonia, cyanosis, cough or total obstruction. Supraglottic foreign bodies usually present with inspiratory wheeze while infraglottic bodies will produce expiratory wheeze. History of a witnessed choking event is suggestive of aspiration.

Decreased breath sounds, rhonchi, wheeze, non-resolving pneumonia are typically late findings of aspiration. A foreign body can impede airflow by four mechanisms: (I) inspiratory one-way valve—air may be inhaled but not exhaled; (II) expiratory one-way ("ball") valve—air may be exhaled but not inhaled; (III) bypass valve—partial obstruction of inhalation and exhalation; (IV) stop valve—total blockage.

Depending upon hemodynamic and respiratory stability of patient, chest radiograph can be obtained to locate the position of the foreign body assuming it is made of radio-opaque material. Tracheal objects tend to align in the sagittal plane (40). Secondary evidence for the presence of a foreign body comprises of atelectasis, air trapping, emphysema or mediastinal shift (41). However, chest radiographs can be normal in 17% of cases or it may not show any evidence during the first 24 hours (40). Lateral radiographs are helpful in identifying objects behind the trachea which reflect as soft tissue swelling and loss of cervical lordosis. CT scan and virtual bronchoscope are more sensitive compared to chest radiographs (42,43). Traditional rigid bronchoscopy can be considered for diagnostic, but also for therapeutic purposes. Two prospective studies compared the use of rigid compared to flexible bronchoscopy in the treatment of foreign body aspiration. Both studies concluded, that patients with clinical signs of asphyxia in combination with radiological findings like evidence of a foreign body, emphysema, and unilateral decreased breath sounds should undergo rigid bronchoscopy (44,45). In contrast, another retrospective study reported a success rate of 91% of removing foreign bodies by flexible bronchoscopy

during a observational period of 8 years and treating 1,027 patients (46). Overall, rigid bronchoscope provides better visualization, control and ventilation whereas the flexible bronchoscope is better suited for foreign bodies in more distal areas due to its flexibility.

However, the choice of rigid or flexible bronchoscopy should be more dependent on personal experience and preference.

Anesthetic considerations

A quick pre-operative assessment followed by imaging might assist in locating the FB. If distal to the carina, the risk of total obstruction is smaller. Organic matter like vegetables or nuts absorb water and swells whereas sharp objects can pierce the airway. Document the time since the last meal. Orogastric tube can be used for aspiration of gastric contents. Time management is crucial, and obvious signs of complete obstruction will indicate an urgent bronchoscopic intervention under anesthesia.

Maintenance of spontaneous ventilation is theoretically important as conversion to positive pressure ventilation can dislodge foreign body causing complete obstruction. Nevertheless, a small prospective trial of 36 patients showed controlled ventilation is more effective than spontaneous breathing (47). Prevention of bucking and coughing is essential. Traditionally, a volatile anesthetic agent (sevoflurane) is preferred over intravenous agents for induction (48), but recently with the development of newer short acting intravenous anesthetics are also gaining popularity, although their use might be associated with increased incidence of laryngospasm and breath holding (49-51). Once adequate depth of anesthesia is reached, a rigid bronchoscope is inserted through the glottic opening. The anesthesia circuit may be attached to the bronchoscope's side arm to allow ventilation (52).

After extraction of the foreign body, the decision to intubate will be guided by the clinical impression of the mucosal membranes—if edema or obstruction is evident, preventive intubation can be performed.

Flexible bronchoscopy can also be utilized in selected cases, and be performed under sedation and topical anesthesia. In uncooperative patients, though, it may require general anesthesia with supra or infraglottic airway control.

Summary

Surgical interventions in the airway can be extremely

challenging for the anesthesia provider, with various considerations that change according to the type and duration of the procedure, anatomical location, patient's comorbidities and the urgency. Meticulous planning and preparing for unexpected events, along with detailed knowledge of the surgical plan are probably the most important factors in the successful administration of anesthesia for these challenging cases. Close cooperation and clear communication between anesthesia and surgery providers remains the most important key to success.

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Footnote

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The anaesthetic consideration of tracheobronchial foreign body aspiration in children

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Abstract: Cases of tracheobronchial foreign body aspiration are frequently encountered emergency cases of childhood; and, delays in its recognition and treatment do result in serious morbidity and mortality. Diagnosis mainly relies on taking history which should indicate what the foreign body is, when it has been aspirated and where it is located. Belated consultation can cause misdiagnosis with the mixing of the symptoms and data with those of other pathologies common to childhood and further delays in the correct diagnosis. Bronchoscopy is required for the differential diagnosis of suspected tracheobronchial foreign body aspiration in order to eliminate other common pediatric respiratory concerns. Given the shared use of the airways by the surgeon and the anaesthesiologist, bronchoscopy is a challenging procedure requiring experienced teams with an efficient method of intercommunication, and also well planning of the anaesthesia and bronchoscopy ahead of the procedures. Despite the recent popularisation of the fiberoptic brochoscopes , the rigid bronchoscopy remains to be used commonly and is regarded to provide the gold standard technique. There have been reports in the literature on the uses of inhalation and/or intravenous (IV) anaesthesia and spontaneous or controlled ventilation methods without any demonstration of the superiority of one technique over the other. The most suitable methods of anaesthesia and ventilation would be those that reduce the risks of complications, morbidity and mortality; and, preventive measures should be taken with priority against childhood cases of tracheobronchial foreign body aspiration.

Keywords: Tracheobronchial foreign body; anaesthesia; child

Introduction

Tracheobronchial foreign body aspiration is an emergency situation with serious life threatening complications frequently met especially in children, such that it probably constitutes one of the most common emergency procedures undertaken in the paediatric population. Early diagnosis and the successful removal of the inhaled foreign material are associated with effective reduction in complications and mortality. Historically, Gustav Killian was the first to use the rigid bronchoscopy method in 1897 to remove a foreign body from the right main bronchus which through the subsequent development of the bronchoscopic techniques lead to the observed reduction in the rate of mortality (1,2). With advances in the anaesthetic technique, rigid bronchoscopy has come to be performed under general anaesthesia. Use of the flexible bronchoscope was started in the 1970s, especially for the removal of aspirated foreign material localised in the distal airways (3,4).

Patients

Tracheobronchial foreign body aspiration is seen most frequently in children under the age of 5 years, the peak incidences varying between 6 months and 3 years of age (5). Generally, the loss of concentration during physical activity, such as running or jumping, while eating or when they

explore plastic or metallic objects they play with by putting them in the mouth can result in sudden symptoms of difficulty in breathing. Given the anatomical characteristics of this age group with the relatively high position of the larynx and epiglottis, narrow airways, compounded with incomplete development of airway protective reflexes, immature swallowing coordination and inadequate chewing process, they run a high risk of this traumatic advent. The risk of foreign body aspiration is more frequent among boys due to their propensity to physical overactivity (5-7).

Clinical presentation and diagnosis

Depending on the type of foreign body, the duration of time after aspiration and the exact location of the object can present with a wide spectrum of clinical symptoms ranging from the asymptomatic to severe respiratory distress (8). Tracheobronchial foreign body aspirations generally present with symptoms of coughing, dyspnea, wheezing, and also very rarely with stridor and cyanosis (9). In cases with delayed diagnosis the unilateral subsidence of breath sounds, audible ronchi, persistent coughing and repetitive pneumonia may be observed. Reported studies have established that the majority of blocking objects are not radiopaque, such that chest radiographs can appear normal, or pulmonary infectious or inflammatory infiltration, mediastinal shift, obstructive emphysema, atelectasis, and air trapping suggestive of foreign body aspiration and very rarely pneumothorax or pneumomediastinum may be observed. The chest X-ray may alter on the basis of object localisation and the aspiration time. Normal X-ray results are usually associated with upper airway obstruction, whereas emphysema and infiltration are seen more in distal airway obstruction. In cases with belated medical consultation, appearance of infection can lead to misdiagnosis and further delays in correct diagnosis. Most of the aspirated objects consist of organic materials, which can vary according to the residential locality of the patient, but often consist of nuts, seeds, and legumes. Materials such as gelatinous snacks that completely obstruct the small cylindrical airways and some types of small toys are exceedingly dangerous (10). In contrast to the inorganic foreign bodies, such as toy parts, pen caps or pins, organic foreign bodies are more inducive to inflammatory reactions and symptoms of fever and pneumonia are observed more frequently (7). Some organic foreign materials may swell due to fluid absorption after aspiration and the partial blockage can become total in time. Also, sharp tipped

objects may perforate the airways they enter (8,11). Taking history leads to correct diagnosis (5). Hence, an aspirated foreign body should be eliminated by procedures of differential diagnosis when there is suspected aspiration or suspicious chest X-ray results, a history of choking crisis, persistent wheezing, and auscultation of unilateral abnormal breathing sounds. Bronchoscopy is demanded when considering the elimination of a possible tracheobronchial foreign body aspiration from other common paediatric pathologies such as asthma, pneumonia, bronchiolitis, upper respiratory tract infections. In cases with clinical emphasis on the presence of an inhaled tracheobronchial foreign body not observable by bronchoscopy, such as with dissolved pills or inhaled talcum powder, histological demonstration of bronchial inflammation on a bronchial biopsy sample could be elected (6).

Management

Most fatalities associated with foreign body aspiration occur during aspiration. Therefore, if an aspiration incident has been witnessed or suspected, basic life support maneuvers based on the guidelines of the European Resuscitation Council and the American Heart Association should be commenced while the local ambulance services are called (6,11). It is imperative that the requisite preparations be completed before bronchoscopy, to be undertaken as early as possible. Bronchoscopy becomes an urgent intervention in severe respiratory distress. If the patient is in a stable condition, it has been recommended that bronchoscopy be performed in day time operating hours with experienced anaesthesiologists and surgeons under optimal conditions (8,11-13). Despite recent preference in some centers for using the fiber-optic bronchoscope, use of the rigid bronchoscope remains the gold standard (7,11,14,15). Although the fiber-optic bronchoscopy has the disadvantages of limited suction and instrumentation, and the lack of ventilatory capability and airway control, it has advantages in being less invasive, and in not requiring general anaesthesia. The flexible bronchoscope is also preferred for the removal of the foreign materials in distal airways of the upper lobe bronchi (8,16-18). It appears more useful with the paediatric patient as a diagnostic device to detect the foreign body, when there is insufficient historical, clinical, or radiologic findings for foreign body aspiration; whereas the rigid bronchoscope is used for its retrieval only (19,20). Presence of an optical forceps on the rigid ventilating bronchoscope simplifies the procedure

as well as rendering it less hazardous. Skill is required for using the rigid bronchoscope in children who have small airways. An appropriately sized bronchoscope has to be selected to avoid the high incidence of bronchospasm in this age group of patients, as well as to prevent laryngeal oedema by not extending the time of the intervention (5). If tracheal blockage and asphyxia are caused during the attempt to remove the foreign body, the rescue technique consists of pushing the object into a bronchus and to ventilate the other lung (7). Care should be taken not to fragment the foreign bodies during its removal as the small pieces may fall into the distal airways creating difficulty of retrieval. After the removal of the main obstructive agent, the trachea, bronchi, the vicinity of the vocal cords and the epiglottis as well as the whole mouth should be checked against the presence of or the remnants of a foreign body. If bronchoscopy is not urgent, the patients should be fasted for at least 6 hours for solids and 2 hours for clear fluids to decrease the risk of aspiration during the procedure; the pre-anaesthetic fasting being important for airway protection against the risk of aspiration, which is difficult to achieve with full stomach (21). If the intervention is urgently required, a large-bore gastric tube can be used to aspirate the stomach contents before induction of anaesthesia (8).

As the airways are used jointly by the surgeon and the anaesthesiologist, a good intercommunication has to be established between them to meet the requirements of the procedure itself and the pre-planning of the anaesthesia and bronchoscopy.

Anaesthetic considerations

Patients should be quiet during induction of anaesthesia to avoid displacement of the inhaled foreign body that may result in complications of further airway obstruction. However, sedative premedication is not warranted in order not to suppress the respiratory drive. Steroids (dexamethasone 0.4–1 mg/kg i.v.) can be used to treat the inflammation and to prevent the likelihood of airway oedema incurred by bronchoscopy (11,22,23). Resorting to the multiple anaesthetic methods during the removal of the foreign body has been reported in the literature. As has been pointed out, positive pressure ventilation during induction can convert the proximal partial obstruction to complete obstruction. Therefore, the common approach with foreign bodies localised proximally is to use smooth mask inhaled induction or cautious IV induction with spontaneous ventilation (8,15). After inserting the bronchoscope through

the glottic opening, spontaneous ventilation may be supported for the cases with proximally located obstructions that seem to require a short procedure of removal. If, however, the procedure is expected to last long with deeper insertion of the bronchoscope, the mobility and reflexes of the patient may have to be suppressed by neuromuscular blocking agents to prevent airway traumas resulting from coughing and resistance as well as to enable the surgeon to work more comfortably (8). With this approach, positive pressure ventilation can be applied to reverse of atelectasis, to correct oxygenation and to overcome the airway resistance. Some anaesthesiologists prefer spraying the epiglottis, larynx and the cords with 1% topical lidocaine before the procedure to reduce the haemodynamic and airway reactions to the introduction of the bronchoscope into the airways, reducing the need for general anaesthetic use and the risks of laryngospasm (11,24). Use of manual jet ventilation during bronchoscopy in nonobstructed lung prevents the hypoxaemia that can arise despite spontaneous or controlled ventilation. Given the tendency in children to fast desaturation, manual jet ventilation reduces the risk of intraoperative hypoxemia (25,26).

Anaesthesia can be maintained by the use of inhaled agents. Sevoflurane is the generally preferred inhalational anaesthetic for fast induction and the least irritatiton to the airways (8,27). Possible gas escapes from the bronchoscope during the procedure necessitate requirement for high gas flows to maintain the depth of anaesthesia, but this may pollute the atmosphere of the operation theatre. Nevertheless, rapidity of induction and recovery and relaxation of the bronchial muscle are distinct advantages (26,27). Constant level of anaesthesia can be achieved with propofol-remifentanil infusion. There are reports of body movement, cough, desaturation and delayed recovery while using different doses of IV propofol-remifentanil with spontaneous ventilation (27,28). Remifentanil infusion can be used together with inhalation anaesthetics. The chosen anaesthesia method can be inhalation or IV based as there is no evidence for the superiority of one approach relative to the other (11). The anaesthetic use and ventilation method (spontaneous or controlled) should ensure the least risks of mortality and complications for the patient (29).

After the removal of the inhaled foreign body, if the patient has not developed any complication relative to his/her general condition before bronchoscopy and also with respect to airway oedema and pulmonary gas exchange, mask ventilation can be applied until adequate spontaneous ventilation is reached. If, on the other hand, a complication has arisen, or the procedure has been prolonged, or there

is residual neuromuscular blockade, the patient is indicated for continued entubation and positive pressure ventilation for re-expansion of any atelectasis, and until completely awake and stabilised with adequate protective reflexes (24).

Postoperative care

Postoperative hospitalisation depends on the clinical state of the patient. Close observation is necessary on the patients who have developed complications before or during the procedure, and treatment should be given on time. For example, if penumonia has developed due to delayed diagnosis, antibiotic treatment should be started immediately. If the patients are stable and have been through uncomplicated procedures, they can be discharged on the same day after a short period of observation.

Complications

Complications may develop due to the tracheobronchial foreign body itself as well as the bronchoscopic procedure. Pneumonia, atelectasis and emphysema are the most frequently observed complications, but laryngeal oedema, complete airway obstruction secondary to dislodged foreign body during coughing or removal, failure to remove the object, hypoxia, hypercarbia, bronchospasm, bradycardia, regurgitation and aspiration of gastric contents, pneumothorax, pneumomediastinum, lung abscess, tracheal laceration, cardiac dysrhythmias and cardiac arrest may also be observed (6,7,24). In delayed diagnosis cases bronchiectasis and irreversible pulmonary changes may develop (10,30). Therefore, early diagnosis and early intervention are highly important.

Conclusions

Tracheobronchial foreign bodies are frequently observed in young children with serious life threatening effects. There is need for preventive measures including parental education and awareness. If not witnessed, treatment for inhaling foreign materials can be delayed as the symptoms are often nonspecific. Suspicious history and symptoms should be taken seriously and bronchoscopy should be performed in order to ensure early treatment and to reduce the development of probable complications including mortality. Bronchoscopy should be performed under optimal conditions after planning by experienced and well cooperating surgical and anaesthetic teams.

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The non-intubated anesthesia for airway surgery

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Abstract: Surgical treatment for lung cancer including airway resection following reconstruction is typically performed under general anesthesia with single-lung ventilation because it is necessary to maintain a sufficient working space and to adjust the airway pressure for the leak test. However, non-intubated thoracic surgery has been gradually developed in recent years for thoracoscopic surgery, due to its lower rate of postoperative complications, shorter hospitalization duration, and lower invasiveness than the usual single-lung anesthesia. Initially, only minor thoracoscopic surgery, including wedge resection for pneumothorax and the diagnosis of solitary pulmonary nodules, was performed under waking anesthesia. However, major thoracoscopic surgery, including segmentectomy and lobectomy, has also been performed under these conditions in some institutions due to its advantages with respect to the postoperative recovery and in-operating room time. In addition, non-intubated thoracic surgery has been performed for tracheal resection followed by reconstruction to fully explore the advantages of this surgical modality. In this article, the merits and demerits of non-intubated thoracoscopic surgery and the postoperative complications, perioperative problems and optimum selection criteria for patients for thoracic surgery (mainly airway surgery) are discussed.

Keywords: Non-intubated; thoracoscopic surgery; airway surgery; feasibility; safety

Introduction

Thoracoscopic surgery has become a standard surgical approach for a variety of thoracic diseases. This approach is regarded as minimally invasive surgery and is performed under tracheal intubation with double lumen tube or bronchial blocker to achieve single-lung ventilation under general anesthesia. Recently, thoracoscopic surgery without tracheal intubation under local and regional anesthesia has been reported to be safe and less invasive for lung, pleura and mediastinum operations than intubated methods. The operative procedures suitable for non-intubated anesthesia have been expanding to include tracheal resection followed by reconstruction. We herein report the feasibility and safety of non-intubated airway surgery.

History of non-intubated anesthesia

Non-intubated thoracoscopic surgery under local and regional anesthesia is an alternative method for treating patients in whom general anesthesia is inappropriate with a poor pulmonary reserve. In such cases, it is difficult to maintain the cardio-pulmonary function with single-lung intubation under general anesthesia.

A double-lumen tube is widely used for single-lung ventilation during thoracic surgery to provide a quiet surgical working space with pulmonary collapse. Before the development of this anesthesia technique, Buckingham *et al*. (1) first reported the use of thoracic epidural analgesia (TEA) to perform awake thoracic procedures in 1950. However, performing awake thoracic surgery is

more technically challenging than the same procedures under general anesthesia, so thoracic surgery is typically performed under general anesthesia with single-lung intubation. In the 1990s, thoracoscopic surgery replaced thoracotomy because of the lower invasiveness and earlier post-operative recovery. With this background, the appropriateness of local and regional anesthesia for thoracic surgery is being investigated once again. Indeed, improvement has been seen in the efficacy of local and regional anesthesia for performing waking surgery. Given that general anesthesia with a double lumen endo-tracheal tube may lead to complications, including accidental airway trauma, hyperinflation of the dependent lung and unilateral ventilator-induced lung injury, alternative methods of achieving anesthesia are awaited.

Techniques of non-intubated anesthesia

Non-intubated thoracic surgery is more technically challenging than thoracic surgery under general anesthesia, but it helps avoid the complications associated with intubation and mechanical ventilation injury (2,3). Several methods combining local and regional anesthesia techniques have been proposed, including local wound infiltration, serratus anterior plane block, selective intercostal nerve blockade, thoracic paravertebral blockade, TEA and lidocaine administration in the pleural space (4). Considering the need for post-operative analgesia, a catheter placement is an even more useful method.

As premedication before anesthesia, intramuscular midazolam and atropine are used for sedation and secretion reduction. During the operation, continuous intravenous sedation and analgesia are needed to relieve patients' anxiety, especially for more invasive and time-consuming procedures. Remifentanil administered as total intravenous anesthesia is useful because of the short context-sensitive half-time of 3 min (4).

With regard to the complications associated with local and regional anesthesia, physicians should be alert for potential lidocaine addiction. Complications associated with epidural anesthesia include dural puncture, neurological injury and paraplegia. The planning of the local and regional anesthesia before each procedure is very important. The procedure and incision site, the expected operation time and the condition of the patient, including their mental situation, should be considered. A continued infusion of sedation and analgesia drugs is administered in order to achieve adequate sedation under spontaneous respiration

and avoid excessive patient hyper-reactivity, apnea or carbon dioxide retention.

Advances in surgical techniques, anesthesia techniques and sedation drugs have enabled thoracic surgery to be performed under non-intubated anesthesia conditions. While this is challenging for anesthesiologists and surgeons, it allows patients to undergo less invasive procedures.

Non-intubated minor thoracoscopic surgery

Since the late 1990s, non-intubated thoracoscopic surgery has been performed as a less invasive procedure for pneumothorax and small nodule resection. Nezu *et al.* (5) reported thoracoscopic wedge resection of blebs with a stapling device under local anesthesia with sedation in 34 consecutive patients with spontaneous pneumothorax. They compared the non-intubated patients' clinical course with that of 38 patients who underwent the procedure under general anesthesia during the same period and concluded that thoracoscopic wedge resection under local anesthesia did not induce an increase in the rates of any perioperative complications and additionally resulted in a shorter hospital stay. In the same period, Mukaida *et al.* (6) reported the usefulness of TEA for the thoracic management of secondary pneumothorax in high-risk patients contraindicated for general anesthesia. Noda *et al.* (7) reported the benefits of awake thoracoscopic surgery in patients with secondary spontaneous pneumothorax using propensity score matching and compared the surgical results between TEA and general anesthesia. They found that the duration of the operating room stay was shorter in the non-intubated group than in the intubated group (P=0.006), and the incidence of postoperative respiratory complications, including pneumonia and acute respiratory distress syndrome, was lower in the non-intubated group than in the intubated group (P=0.02).

Pompeo *et al.* reported on the outcomes of non-intubated surgery for wedge resection of solitary pulmonary nodules, pneumothorax and non-resectional lung volume reduction (8-10). They also performed a randomized study of thoracoscopic surgery with talc pleurodesis using TEA or general anesthesia (11). They emphasize the safety and feasibility of non-intubated thoracoscopic surgery. In each analysis, they concluded that non-intubated thoracoscopic surgery reduced the hospital stay, morbidity rate and procedure-related costs relative to the procedures performed with general anesthesia.

Regarding other reports of non-intubated thoracoscopic

surgery, Mineo *et al.* (12) performed a case-matched study of pleurodesis for malignant pleural effusion comparing the outcomes between non-intubated and intubated thoracoscopic surgery. Liu *et al.* (13) performed a randomized control trial in 354 patients (167 patients in the non-intubated group and 180 in the control group) comparing the outcomes between non-intubated and intubated thoracoscopic surgery. The surgical procedures included bullae resection, pulmonary wedge resection and lobectomy. The non-intubated group had markedly lower rates of postoperative mortality (6.7% *vs.* 16.7%, P=0.004) and respiratory complications (4.2% *vs.* 10.0%, P=0.039) than the intubated group. They emphasized the merits of non-intubated anesthesia as a shorter hospital stay and lower cost.

Non-intubated major thoracoscopic surgery

Thoracoscopic surgery has expanded globally as a minimally invasive alternative to thoracotomy because of its low invasiveness and painless aspect following surgery (14). This technique has also been applied in lobectomy for early-stage lung cancer. To further improve these surgical procedures, Chen *et al.* (15,16) reported on the outcomes of lobectomy for lung cancer patients performed as non-intubated thoracoscopic surgery. Non-intubated anesthesia for major thoracoscopic surgery is limited to the non-problem cardio-pulmonary function and pursue the minimum invasive surgery. As such, non-intubated anesthesia cannot be adapted for major thoracoscopic surgery in the same way as for minor thoracoscopic surgery. Chen *et al.* evaluated the feasibility and safety of non-intubated thoracoscopic lobectomy using TEA, intrathoracic vagal blockade and sedation. They found that the patients who underwent non-intubated surgery had lower rates of sore throat (P=0.002) and earlier resumption of oral intake (P<0.001) than those who were intubated. Patients undergoing non-intubated surgery also tended to have better non-complication rates and shorter postoperative hospital stays than those who were intubated (15). They additionally reported the outcomes of 36 consecutive elderly patients with stage I and II non-small cell lung cancer who underwent thoracoscopic lobectomy under non-intubated anesthesia, confirming the safety and feasibility of non-intubated anesthesia even in elderly patients (16).

However, several issues remain to be resolved regarding the use of non-intubated TEA for major pulmonary resection. Careful patient selection is needed in order to avoid complications of hypoxia and hypercapnia. To avoid perioperative respiratory failure, non-intubated

TEA is usually performed only in certain patients, namely those who can tolerate an estimated operation time of up to 3 hours and have ASA grade I-II, body mass index <25, and a good cardiopulmonary function (17). Chen *et al.* (15) reported that 3 patients (out of 30) in the non-intubated group required conversion to intubated single-lung ventilation because of persistent hypoxemia, poor pain-control and bleeding. Non-intubated thoracoscopic segmentectomy for lung tumors has also been reported, and the rapid recovery after surgery and reduced anesthesia costs have been confirmed (18-20).

Non-intubated surgery for the upper trachea

Especially for upper airway surgery, tracheal surgery is usually performed under general anesthesia, with the cessation of spontaneous breathing, and cross-field intubation with intermittent ventilation is the most common method for resection and reconstruction of the trachea. Macchiarini *et al.* (21) reported the feasibility of upper airway surgery under awake anesthesia and spontaneous respiration. They managed patients with upper tracheal stenosis through cervical epidural anesthesia and conscious sedation with atomized local anesthesia. They experienced only one case who required a nasotracheal tube for 36 h after the surgical procedure. They treated the patients with idiopathic or postintubation upper tracheal stenosis and concluded that awake and tubeless upper airway surgery is feasible and safe and has a high level of patient satisfaction. They emphasized that non-intubated airway surgery not only avoids general anesthesia with tracheal intubation and mechanical ventilation but also provides an ideal surgical field without any intraoperative tubing systems. Furthermore, the maintenance of spontaneous breathing makes airway reconstruction more anatomical and enables checking the movement of vocal cords during the surgical procedure, with an earlier recovery. Liu *et al.* (22) reported a case of non-intubated tracheal resection and reconstruction for the treatment of a mass in the upper trachea via neck incision. The resection of adenoid cystic carcinoma (ACC) was done under intravenous anesthesia plus cervical plexus local anesthesia using a laryngeal mask. The patient remained awake during the surgery, and the depth of anesthesia was measured using the electroencephalogram bispectral index. They emphasized the following merits of non-intubated tracheal resection: the patient retained spontaneous breathing, endo-tracheal intubation was not necessary and the time of tracheal suture was shorter than

in cases requiring operative field intubation.

For upper tracheal surgical procedures under local and regional anesthesia, switching to general anesthesia and intubation in the operating field is quite easy if preparations have been made in advance, as the operation field for the upper trachea is closer and wider than with an intrathoracic approach for the lower trachea.

Non-intubated surgery for the lower trachea

Bronchial sleeve resection has emerged as an effective but complicated thoracoscopic approach to avoid pneumonectomy and maintain the left lung function in order to reduce the procedure-related mortality and morbidity rates. Shao *et al.* (17) reported a case of complete endoscopic bronchial sleeve resection of right lower lung cancer under non-intubated epidural anesthesia. Intramuscular midazolam and atropine were administered 30 min before anesthesia. Epidural anesthesia was administered into the T7-8 intervertebral space, with the epidural catheter tip pointed towards the head and fixed after confirming successful placement, and an adequate dose of the drug was administered. To keep the airway open in order to supply oxygen, a laryngeal mask airway (LMA) was inserted, and the anesthesia machine was connected to provide simultaneous intermittent mandatory ventilation. To suppress the cough reflex caused by lung tissue stretching during the intra-thoracic procedure, an intrathoracic vagus nerve block was added. Part of the intermediated bronchus was resected, and the right middle lobular bronchus was joined with the right intermediated bronchus. The operation time was 165 min, and it took 25 min to perform bronchial anastomosis. Maintaining oxygenation while the intermediate bronchus is open seems difficult. It is therefore necessary to prepare the intra-operative field properly or switch to endo-tracheal intubation and general anesthesia for this procedure.

Non-intubated surgery for the carinal reconstruction

Carinal resection and reconstruction is one of the most difficult and challenging surgeries for thoracic surgeons. Peng *et al.* (23) reported the outcome of non-intubated complete thoracoscopic surgery for carinal reconstruction in a patient with ACC of the trachea. Pre-anesthesia preparation included the use of midazolam and atropine 30 min before surgery. TEA was performed at the T6-7

level, and intravenous anesthesia was performed using remifentanil, dexmedetomidine and propofol as sedation to maintain spontaneous breathing. To keep the airway open in order to supply oxygen, an LMA was inserted, and local anesthesia with lidocaine, an intercostal nerve block and a vagus nerve block were also used. Peng *et al.* concluded that carinal reconstruction under non-intubated anesthesia is a feasible and safe method of anesthesia for certain patients, but they could only draw conclusions based on their single experience of carinal reconstruction under local and regional anesthesia. The feasibility and safety should therefore be confirmed in more patients in order to establish appropriate criteria for identifying candidates for this procedure.

Problems with non-intubated airway surgery

There are several issues that must be addressed with airway surgery under non-intubated anesthesia. The first issue concerns the management of hypoxia, especially after cutting open the airway. High-flow oxygen has been delivered via a laryngeal mask to maintain a high oxygen concentration in the pleural cavity, but this technique has limitations. The burst by using electrosurgical knife should be aware during such situation. The second issue concerns the management of hypercapnia and continuous measurement of the carbon dioxide level during airway reconstruction. The third issue concerns how to perform the air-leak test after reconstruction, as adequate positive pressure management is impossible under non-intubated conditions. Fourth, blood and secretions dropped into the airway during reconstruction cannot be removed via suctioning under non-intubated conditions. Peng *et al.* reported that the operator must perform adequate hemostasis before anastomosis in order to ensure that the surgical field is clean. Fifth, and the most important issue, coughing during airway construction must be prevented, as severe complications may occur due to patient movement during airway suturing. Shao and Peng have described the effectivity of the vagus nerve block in the intra-thoracic field to suppress the cough reflex (22,23). Finally, airway surgery is still an extremely risky operation, and the outcomes of few cases have been reported. Educating younger surgeons is an important duty for experienced surgeons.

Safety and guidelines for non-intubated thoracoscopic surgery

Non-intubated thoracic surgery is challenging. To perform

lobectomy and airway surgery under spontaneous respiration, the team (surgeons, nurses and anesthesiologists) should have experienced the same procedure under general anesthesia as well as have performed the easier method of thoracoscopic surgery before, including wedge resection and pleural infiltration cases. The entire team must be aware of the complications that can happen during awake thoracic surgery, with potential risks including hypoxemia, uncontrolled cough and severe bleeding. If the patient must be emergently intubated during non-intubated thoracic surgery, the anesthesiologist must be trained in lateral intubation. Navarro-Martinez et al. (24) reported that they trained themselves to intubate in the lateral position using scheduled-surgery patients. They emphasized that responses to surgical and medical emergencies during non-intubated thoracoscopic surgery must follow the crisis resource management guidelines. Before beginning non-intubated surgery, the surgical team should confirm the criteria for conversion to general anesthesia and not hesitate with such conversion.

Conclusions

Cases of non-intubated airway surgery are not very frequent, and the merits of non-intubated airway surgery over intubated surgery remain unclear, especially for carinal reconstruction and lower tracheal resection and reconstruction. The mortality rate for tracheal resection and reconstruction is still high, and few cases have been reported. This dearth of reports hampers the widespread application and further development of the technique. At present, we can cite no overwhelming benefit to non-intubated airway surgery outweighing the associated risks. As such, non-intubated thoracoscopic surgery should be limited to lobectomy for the time being.

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Footnote

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Surgery of the airway: historic notes

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Abstract: Prior to the 20th century, the need for surgical procedures on the airway was infrequent and consisted mainly of tracheostomy to relieve airway obstruction or repair of tracheal injuries such as lacerations. Even the ability of tracheal suture lines to heal primarily was viewed with concern due to the rigidity of the tracheal wall, its precarious blood supply and uncertainty as to whether the cartilage components could heal without complications. In the 20th century the evolution of tracheal procedures on major airways evolved to meet the challenges provided by the expanding fields of thoracic surgery and advent of mechanical respiratory support with its associated complications. In the first half of the century lobar and lung resections done for tuberculosis and lung cancer required methods for safe closure of the resulting bronchial stumps and end-to-end bronchial anastomosis in the case of sleeve resections of the lung. Beginning in mid-century the advent of respiratory care units for the treatment of polio and for the expanding fields of thoracic and cardiac surgery resulted in a significant number of post-intubation tracheal stenosis requiring resection and primary repair. In the last 20 years of the century the development of lung transplantation with its requirement for successful bronchial anastomoses between the donor and recipient bronchi, created unique challenges including ischemia of the donor bronchus the adverse effects of immunosuppression, donor lung preservation and diagnosis and management of post-transplant infection and rejection.

Keywords: Tracheal resection; bronchial anastomosis; tracheal bronchial surgery

Surgery of the airway has its roots in ancient history but its major developments have occurred in the last 60 years.

The oldest recorded surgical procedure on the airway is in the *Edwin Smith Papyrus an ancient Egyptian medical text* thought to date around 1600 BCE. The papyrus is primarily concerned with traumatic injuries and their treatment and demonstrates a procedure thought to be a tracheotomy to provide an emergency airway. References to tracheostomy were also made in the Greek literature and the use of a tube placed through a tracheostomy was noted in the 4th century BCE (1). Until the early part of the last century, surgery of the airway was confined primarily to tracheostomy to relieve upper airway obstruction such as for diphtheria, or for repair of traumatic injuries, such as lacerations, to the trachea. Several authors have chronicled the history and evolution of tracheostomy procedures (1-3).

The advent of elective surgical procedures for the resection and reconstruction of the major airways began in the mid portion of the last century. Progress was hampered by technical and biologic factors peculiar to the airway as well as by infrequent need for such procedures.

In 1881 Glück and Zeller (4) were able to demonstrate healing end-to-end after tracheal anastomosis in dogs and in 1886 Küster successfully performed a primary tracheal anastomosis of the cervical trachea after resecting a segment for post-traumatic stenosis (5). In the early part of the last century animal studies confirmed that end-to-end anastomoses following bronchial or tracheal resection could heal. Human experience with satisfactory bronchial closure after lobectomy or pneumonectomy confirmed the importance of fibrous tissue repair on the outer portion of the airway as an important component in the satisfactory

healing of wounds, incisions and anastomoses of the airway. Success in repair of war-time injuries to the bronchus in World War II (6) and subsequent successful end-to-end bronchial anastomoses for sleeve lobectomies (7) confirmed the potential for satisfactory healing following anastomosis of the major airways (7-9).

Belsey, in a manuscript entitled "Resection and Reconstruction of the Intrathoracic Trachea" in 1950, observed that "the intrathoracic portion of the trachea is the last unpaired organ in the body to fall to the surgeon, and the successful solution of the problem of its reconstruction may mark the end of the 'expansionist epoch' in the development of surgery" (10). Belsey noted that among factors inhibiting successful surgical procedures on the trachea were centuries-old concerns regarding the poor-healing properties of the trachea. These admonitions related to poor blood supply, rigidity of the cartilaginous rings which interfered with easy, tension free apposition of wound edges, and the technical difficulties of operating on the trachea without suspending its essential role of providing a conduit for ventilation of the lungs. Belsey noted the absence of a satisfactory means of surgically bypassing portions of the trachea contrary to methods of bypassing other conduits such as the bowel and blood vessels. He also postulated that if trachea replacement were to be possible, a substitute would require a laterally rigid but longitudinally flexible tube and would ideally have an inner surface of ciliated respiratory epithelium.

By the mid-1950s it was well established that closure of bronchial stumps following lobectomy, and end-to-end bronchial anastomoses and broncho-plastic procedures for lung preserving pulmonary resections could be performed with good results, as reported by Paulson and Shaw in 1955 (11). However there was still a perception that only very limited lengths of trachea could be resected with primary anastomosis (4,12). Concerns related to the ability of tracheal cartilage to heal, the adverse effects of anastomotic tension on anastomotic healing and the tenuous blood supply to the trachea. In addition, in the 1950s, the indications for a tracheal resection were limited, consisting mainly of tracheal tumors which were often deemed unresectable, or which would require a resection length greater than the widely perceived 2 cm limit for safe tracheal resection. Furthermore at that time the anesthetic techniques for conducting intrathoracic resection of the trachea while maintaining adequate ventilation were not well-developed. Thus the stimulus for expanding the techniques and limits of tracheal resection

was lacking. All of that was to soon change however due to the worldwide epidemic of poliomyelitis in the early 1950s which initiated the era of positive pressure ventilation through cuffed endotracheal or tracheostomy tubes. Over the ensuing decade respiratory intensive care units were initiated, initially for ventilatory assistance for patients with neurologic disorders, such as Polio, Myasthenia Gravis, Guillain Barre Syndrome, strokes, etc. The burgeoning of thoracic surgery and cardiac surgery expanded the need for postoperative positive pressure ventilation and this experience in turn further stimulated progress in anesthetic techniques, the development of more sophisticated ventilators, the field of respiratory therapy and the routine application of ventilatory assistance in specialized medical and surgical intensive care units. In the mid-1960s however, the hospital mortality rate for patients requiring ventilatory assistance was between 30–50%. Furthermore, amongst the survivors 20% or more developed airway complications, primarily tracheal stenosis. This situation set the stage for investigation and clinical application of techniques to extend the safe limits of tracheal resection. Cadaveric studies were undertaken to elucidate the blood supply of the trachea, and demonstrated the lateral position of the arterial supply which in turn fed the small segmental vessels to the trachea (13,14). Mobilization techniques to reduce anastomotic tension focused on the arterial anatomy and included anterior and posterior blunt mobilization of the trachea down to the carina augmented by the inherent elasticity of the trachea itself. Mobilization of the carina by means of right hilar dissection and division of the right pulmonary ligament, and laryngeal release at the upper end of the trachea further extended the limits of safe tracheal resection. Dedo and Fishman, in 1969 described the thyro-hyoid laryngeal release as an adjunct to resections for tracheal stenosis (15). In 1974 Montgomery described the suprahyoid release, which is now the most widely accepted form of laryngeal release in terms of efficacy, reduced morbidity and technical simplicity (16).

A cadaver study by Mulliken and Grillo, reported in 1968, demonstrated that the combination of cervical and mediastinal mobilization of the trachea, together with flexion of the neck by 15 to 35 degrees, resulted in an average of 4.5 cm of trachea that could be resected with end-to-end approximation with no more than 1,200 grams of tension applied to the divided ends of the trachea (17). The addition of right hilar dissection and intrapericardial mobilization at the lower end, and laryngeal release at the upper end, could facilitate even more aggressive resection.

Between 1965 and 1971 a series containing a large numbers of tracheal resections were reported, most for post-intubation tracheal stenosis (13,18-28). This in turn focused attention on the need to prevent such post-intubation injuries.

In 1965 the author (Cooper) was a surgical resident at the Massachusetts General Hospital, where Dr. Hermes Grillo was director of the general surgery training program. At his suggestion and with his guidance, an autopsy study was undertaken whereby patients dying while receiving ventilatory assistance would have the existing tracheostomy or endotracheal tube secured in place for the subsequent autopsy dissection, contrary to the usual custom at the time of removing all tubes and catheters prior to sending the deceased patient for autopsy. This permitted excision of the larynx and entire trachea with the tube in place allowing correlation between the tip of the tube, the location of the cuff etc., with any underlying adjacent changes observed in the airway. For the 30 post-mortem examinations so conducted, the duration of intubation ranged from 1 to 60 days. A spectrum of lesions were seen at the cuff site with superficial tracheitis and mucosal ulceration apparent after a few days of intubation followed by exposure and infection of cartilaginous rings after a few more days. The final stage of cuff injury included fragmentation and loss of cartilage resulting in an unsupported, ulcerated and inflamed segment of trachea. It was presumed that the subsequent development of tracheal stenosis in survivors of ventilatory assistance was due to cicatricial scarring and constriction of this damaged unsupported segment (29). Other reports also pointed to tracheal injury at the cuff site as a possible cause of tracheal stenosis (30) including a prospective bronchoscopic evaluation of 103 patients receiving ventilator support conducted by Andrews and Pearson (31). The exact cause of this localized damage at the cuff site however had not been determined and was variably attributed to the nature of the cuff material, the exposure of the cuff to gas sterilization prior to its use, infection and pressure necrosis. In the previously noted autopsy study reported by Cooper & Grillo, the intracuff pressure necessary to inflate the cuff on the endotracheal tube or tracheostomy tube to an occlusive volume was measured and was in the range of 200 mm of mercury. Such high intracuff pressure is primarily related to the force required to distend the cuff, and not necessarily to the pressure applied to the adjacent tracheal mucosal. The intracuff pressure, however, does correlate with the rigidity of the inflated cuff and the resulting pressure it places on the adjacent trachea, which has to conform to the shape of the cuff

to create a seal. However with a large volume, low pressure cuff, the cuff is easily deformed and adapts its shape to that of the adjacent trachea creating a seal with very little force on the trachea itself. In 1943, Grimm & Knight had suggested that an ideal intra-tracheal tube cuff "should have sufficient volume when inflated without stretching to fill the diameter of the trachea" (32).

On the basis of the findings of their autopsy study, Cooper and Grillo designed an experimental canine model to compare the effect of the standard cuffs with that of a large volume, thin walled, latex cuff. Each cuff was mounted on a segment of an endotracheal tube and implanted in a dog's trachea. The cuff was kept inflated to produce an airway seal between the cuff and the trachea at an airway pressure of 20 cm of water. After a week of exposure the low pressure cuff produced no mucosal damage, compared to the use of the standard, elastic, high pressure cuff then in use, which resulted in the same type of ulceration, cartilaginous fragmentation, and loss of tracheal support, observed in the human post mortem studies (33). A subsequent randomized clinical trial comparing experimental low pressure tracheostomy tube cuffs with the standard cuffs confirmed the role of pressure necrosis at the cuff site caused by the standard cuff and the absence or marked reduction in tracheal injury with the low pressure cuff.

A second type of post-intubation tracheal stenosis relates to damage at tracheostomy stomal site. Stenosis at this site is due to the loss of the anterior supporting arch of the tracheal rings with subsequent inward collapse of the lateral tracheal walls, resulting in the so-called "A-frame" deformity. Unlike circumferential strictures at the cuff site, stomal strictures involve scarring and narrowing only on the anterior wall of the trachea at the stomal site whereas the lateral and membranous walls remain mobile. This generally results in preservation of the A–P dimensions of the trachea, with marked side to side narrowing. This situation may not produce symptoms for even decades. During this interval the anterior wall angulation may act as a hinge allowing the sidewalls to easily move laterally with respiration. However, with time the lateral walls may become fixed in a more central position leading to symptoms. In a recent case, a 75-year-old man presented with acute, severe stridor and airway obstruction having essentially been asymptomatic for the 70-year interval following a temporary tracheostomy for upper airway obstruction at age 5. The risk of such a stenosis increases with the size of the tracheostomy tube used and may be further augmented by enlargement of the stoma due to traction on the tracheostomy tube by the

attached ventilator tubing. With the use of a lightweight, flexible, swivel tracheostomy tube connector between the tracheostomy tube and the ventilator tubing, Andrews and Pearson observed a reduction in the incidence of stomal stenosis from 17.5% to 6.9% (31).

Concurrent with the development of techniques to extend the limits of tracheal resection, increasingly complex resections were developed for tumors involving the carina and main bronchi. A number of reconstruction methods were used depending on the exact extent of tumor involvement of the distal trachea and main bronchi. This included side-to-side anastomosis between the two main bronchi which were then attached end-to-end to the distal trachea; end-to-end anastomosis between the trachea and the left main bronchus with implantation of the right main bronchus into the right lateral aspect of the trachea; end-to-end anastomosis between the trachea and the right main bronchus with attachment of the left main bronchus to the side of the right intermediate bronchus, and others. Such procedures not only present technical challenges, but require close coordination between the surgeon and an experienced anesthesiologist using a variety of techniques including high-frequency jet ventilation, intermittent ventilation and cross-table ventilation with an endotracheal tube placed into one or other main bronchus by the surgeon. In general the use of cardiopulmonary bypass has not been employed out of concern that extensive manipulation of the lung during the anticoagulation required for bypass might lead to parenchymal hemorrhage, pulmonary edema and the need for postoperative ventilatory assistance, which poses a significant risk to patients undergoing any type of airway reconstruction.

Bjork in 1959 (34) reported on a series of bronchotracheal anastomoses and subsequent series of successful carinal resections were reported by Eschapasse in 1974, Perelman in 1980 and Grillo in 1982 (35-37). Several other reports focused on the anesthetic challenges and their management for complex trachea-bronchial reconstructions (38-42).

Just as resections at the distal end of the trachea require more complicated techniques than tracheal resections alone, special techniques were also required for proximal conditions involving the upper end of the airway and the subglottic region. These require resection of the proximal end of the trachea with anastomosis to the larynx for traumatic injuries, damage to the subglottic region from endotracheal tubes and idiopathic subglottic stenosis. Such resections often require an anastomosis within a centimeter of the vocal cords and create a significant risk for damage

to one or both recurrent laryngeal nerves. Traditionally, and even up to the present time, many of the procedures performed by Otolaryngologists, involve repeated dilatation, laser ablation, advancement of mucosal flaps, free mucosal flaps and anterior and/or posterior cricoid split with insertion of a wedge of bone or cartilage in an attempt to enlarge the narrowed passageway. In general these have had only limited success. The development of techniques for primary resection and end-to-end anastomosis of the airway to the larynx with sparing of the recurrent laryngeal nerves has proven to be an excellent alternative. Shaw, in 1961, reported two patients with traumatic tracheal rupture treated by cricoid resection with anastomosis to the thyroid cartilage. In these patients the vocal cords were already paralyzed (43). Gerwat and Bryce at the Toronto General Hospital reported resection for laryngeal stenosis with partial cricoid resection and anastomosis of the trachea to the lower border of the thyroid cartilage anteriorly and to the cricoid lamina posteriorly, inferior to the cricoarytenoid joint (44). This was carried out only after carefully identifying the recurrent laryngeal nerves and tracing them up behind the cricothyroid joints before horizontally transecting the cricoid lamina posteriorly. The procedure incorporated a laryngeal release to reduce tension by mobilizing the laryngeal end of the anastomosis. A protective tracheostomy was placed and maintained for 2–3 weeks to reduce the danger of aspiration.

In 1975, Pearson and colleagues, also at the Toronto General Hospital, described a new method for resecting the airway at the cricoid level with preservation of the recurrent laryngeal nerves (45). This involved a line of transection which begins at the inferior border of the thyroid cartilage anteriorly and is carried obliquely down to transect the airway posteriorly through the upper end of the membranous trachea just at the inferior border of the cricoid lamina. The lamina is then reamed out using fine rongeurs, preserving the stout perichondrium on the backside of the lamina to avoid injury to the underlying laryngeal nerves. The perichondrium and the airway mucosa lying on the anterior surface of the cricoid lamina is also preserved but is transected at a more proximal level as necessary to get proximal to the damaged portion of the airway. By coring out the inferior portion of the thick cricoid lamina, the subglottic airway is thus enlarged allowing the trachea to be brought up for a primary anastomosis to a level up to 1 cm below the vocal cords. If necessary the membranous wall of the trachea is plicated to bring the tips of the upper tracheal ring together. This reduces the diameter and also

forms a complete circle of cartilage for increased stability. The initial description of this procedure also incorporated laryngeal release to reduce anastomotic tension and a protective tracheostomy for 1–2 weeks postoperatively. This procedure was soon adopted by other centers as it provided an attractive solution to the problem of benign traumatic or post-intubation injury to the subglottic region. In most cases laryngeal release is found to be unnecessary and a protective tracheostomy is seldom required. Grillo and coworkers subsequently reported excellent experience with this procedure in 18 patients and in some cases modified the procedure by not coring-out the inferior portion of the cricoid lamina, but rather excising damaged airway mucosa on its anterior surface, and resurfacing this part of the airway with a broad-based flap of posterior membranous trachea wall shaped for that purpose (46). At the present time resection of the subglottic airway is most commonly employed for the treatment of idiopathic subglottic stenosis and for post-intubation injuries affecting the region of the cricoid cartilage and upper trachea. Such injuries may occur from placement of a tracheostomy site too high in the airway, either through or just inferior to the cricoid arch. This may occur inadvertently, but may also result from performance of an emergency tracheostomy in a life-threatening situation or from an elective tracheostomy in a patient with adverse anatomy such as kyphosis, obesity or other conditions limiting access to the trachea at the desired level.

Until the mid-1980s, airway anastomoses involving the trachea or main bronchi were almost exclusively related to repair and/or resection of a portion of the airway. Since then however, the most common need for end-to-end airway anastomosis relates to the airway connection made for lung transplantation usually at the level of the main bronchi. Such anastomoses are not under tension, do not pose significant technical challenges, and do not require fancy reconstruction techniques or mobilization of either proximal or distal ends of the anastomosis. Nonetheless, complications of this relatively straightforward airway anastomosis posed one of the major obstacles to successful lung transplantation making it the last of the vital organ transplants to be relatively successful.

The first attempt at human lung transplantation was by Dr. James Hardy in 1963 (47). This followed almost two decades of experimental work on lung or lobar transplantation conducted in many laboratories. Dr. Hardy's patient survived 18 days with death attributed to renal failure and malnutrition. Between 1963 and 1978

approximately 38 lung or lobar transplants were attempted around the world. Thirty-seven patients died in hospital and only one patient, following a prolonged postoperative stay, did leave hospital with limited benefit for the remaining months of his survival (48). Review of this world experience revealed that of the nine patients who survived more than 2 weeks following transplant, six died of dehiscence of the bronchial anastomosis and the remaining three had airway complications at the anastomotic site. Although many other issues related to lung transplantation remained to be resolved, complications at the bronchial anastomosis site became the cause of continued discouragement and the primary focus of ongoing research. There was widespread belief that rejection was playing a major role without any obvious remedy in sight. Immunosuppression following organ transplantation in that era consisted primarily of high doses of prednisone and azathioprine. It was recognized that interruption of the bronchial arterial supply by the transection of the donor bronchus left the donor end of the bronchial anastomosis ischemic. However it was clinically well established that sleeve resection of a lobe, which also involves an end-to-end bronchial anastomosis, was not associated with this type of consistent failure, nor was canine auto transplantation with complete excision of the lung followed by its reimplantation. In neither case was there the inevitable pattern of necrosis and anastomotic disruption observed following human lung transplantation.

At the University of Toronto, after more than a decade of laboratory investigation led by Dr. F.G. Pearson and colleagues, an initial attempt at clinical lung transplantation was made in 1978. This is involved a 19-year-old man who remained on chronic ventilatory support 6 months after an inhalation injury related to a house fire. Under the direction of Nelems, a right lung transplant was performed. The patient was weaned from ventilatory support during the first 2 postoperative weeks, but died on the 17th postoperative day of bronchial dehiscence (49). This outcome, coupled with the almost universal occurrence of bronchial anastomotic complications with patients who survived more than 2 weeks following lung transplantation, prompted a series of laboratory investigations into factors influencing bronchial anastomotic failure in a canine model of lung transplantation. Three potential factors were initially selected for evaluation, namely ischemia, the effects of immunosuppression and the potential influence of rejection.

To eliminate any factors associated with rejection, a series of canine lung auto-transplants were conducted with half of the animals receiving immunosuppression with

prednisone and azathioprine and the other half receiving no immunosuppression. In the immunosuppressed animals, the same constellation of bronchial anastomotic complications including necrosis and disruption were seen. In animals receiving no immunosuppression, the bronchial anastomosis generally healed in primary fashion but with a significant incidence of moderate airway stenosis involving the distal side of the bronchial anastomosis. Further studies conducted on the effects of immunosuppression on bronchial anastomotic healing confirmed that it was the high-dose steroid that was primarily responsible and that azathioprine alone had no adverse effect on healing (50). Further studies showed that the then experimental immunosuppressive drug cyclosporine-A also had no adverse effect and could be substituted in the early post-transplant period for high-dose prednisone, resulting in much improved anastomotic healing (51).

The presence of bronchial anastomotic stenosis following canine auto transplantation in the absence of immunosuppression was thought to be the result of ischemia at the level of the distal bronchus due to transection of the bronchial artery supply during extraction of the lung. This leaves the reimplanted bronchus dependent on retrograde collateral bronchial artery circulation from intra-parenchymal connections between the pulmonary and bronchial circulations. The use of an omental pedicle wrap around the bronchial anastomosis at the time of reimplantation was found to restore systemic bronchial arterial circulation within a very short period of time and resulted in much improved anastomotic healing. In a series of canine lung auto transplantation, without the use of an omental wrap, the cross-sectional area of bronchial anastomosis was reduced by 53% whereas with the use of bronchial omentopexy the reduction in area averaged only 19% (52).

Subsequently a series of canine lung transplants was performed using an omental wrap around the bronchial anastomosis, and azathioprine and cyclosporine-A for initial immunosuppression with the introduction of prednisone in the second week. Six animals were euthanized between 100 and 135 days following transplant and all showed excellent healing of the airway anastomosis with little, if any narrowing (53).

In 1981 Reitz and co-workers at Stanford University initiated a heart-lung transplant program for patients with pulmonary vascular disease. Their success confirmed the ability of lung transplants to provide excellent pulmonary function to patients with end-stage lung disease and also demonstrated a much lower incidence of airway anastomotic complications then had previously been demonstrated with human lung transplantation (54). This improvement was attributed to preservation of the direct connections between the coronary circulation and the bronchial arterial circulation by way of the pericardial vessels which communicate with both systems. The use of cyclosporin-A for the heart-lung transplants may in retrospect also have played a role.

Encouraged by the success of the Stanford heart-lung program and by the laboratory success with canine lung transplantation, the University of Toronto embarked on a human-lung transplant program beginning in 1983. The long-term success of the initial two patients was subsequently reported (55). Over the ensuing years increasing experience with lung transplantation around the world, contributed to rapid improvements in the lung transplantation including donor and recipient selection, improved immunosuppression, improved methods of lung preservation and improved post-operative management. Early extubation following lung transplant is now commonplace. In retrospect it is apparent that the same issues that slowed progress with resection and reconstruction of the trachea and bronchi were also at play in the development of human lung transplantation, namely factors affecting wound healing at the anastomotic site. With tracheal and bronchial resection these factors included ischemia and tension from the anastomosis. With transplantation it was ischemia, adverse effects of immunosuppression and the prolonged postoperative ventilatory assistance required in the early days of lung transplantation. With lung transplantation, the omental wrap, which provided a "security blanket" around the anastomosis was no longer employed after several years. Improved lung preservation including both antigrade and retrograde pulmonary flushing at the time of donor extraction almost certainly improved the collateral blood flow from the pulmonary to bronchial vessels. This coupled with improved postoperative management and marked improvement in diagnosis and management of rejection has reduced the incidence of serious airway anastomotic complications following lung transplantation to 5% or less.

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Trachea and Bronchi" served as an invaluable resource in the preparation of this article. The 900 pages of his textbook, which, as he once remarked, amounts to about 75 pages for each centimeter of the average trachea, testifies to the patient, persistent and methodical approach he brought to the development of modern day airway surgery.

Footnote

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Tracheal resection and reconstruction for malignant disease

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Abstract: Malignant tracheal neoplasms are rare diseases, mostly represented by squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC). Symptoms presentation is often misleading and diagnosis may be delayed for months or years, so clinical suspicion plays a fundamental role. Corner stones in the diagnostic pathway are represented by rigid endoscopy and computed tomography (CT) scan, necessary to correctly stage the patients and identify the optimal surgical candidate. When appropriate, surgical resection and reconstruction is still the best opportunity to achieve a long-term survival with a good quality of life, but this kind of surgery is always a very challenging procedure and a wide experience with an in-depth knowledge of every technical detail, from selection of patient, to choice of surgical approach to reconstruction techniques, are needed and recommended.

Keywords: Tracheal cancer; tracheal resection; tracheal surgery; adenoid cystic carcinoma (ACC); squamous cell carcinoma (SCC)

Introduction

Primary neoplasms of trachea are rare and uncommon malignancies, that account for less than 0.01% of all tumours and for about 0.2% of respiratory malignant lesion, representing a low rate of all airway neoplasm deaths (1-3).

The most common histologic types are squamous cell carcinoma (SCC), representing about 50–66% of all tracheal tumours, and adenoid cystic carcinoma (ACC), accounting for 10–15% of them (4), with wide different percentages in many clinical and epidemiological series (5-8). Several malignant histologies, of different grade, have also been described, as mucoepidermoid carcinoma, non-squamous bronchogenic carcinoma, sarcoma, carcinoid tumours, melanomas (8,9).

Squamous cell carcinoma (SCC)

SCC usually originates from the membranous pars, with polypoid (*Figure 1*) or ulcerative morphology, more often in distal portion, with a peak incidence between the 6th and 7th decades. As pulmonary SCC, there is a heavy correlation with smoking habits. When local progression occurs, the tumour may infiltrate the surrounding tissue, as larynx, recurrent laryngeal nerves or esophagus, while paratracheal lymph nodes are often sites of loco-regional metastasis.

Reported 5- and 10-year survival rate is about 40–50% and 20–30%, respectively (7,10).

Adenoid cystic carcinoma (ACC)

ACC may present as a polypoid lesion (*Figure 2*) or show an infiltrating growth of the tracheal wall, more often in proximal portion, at submucosal and perineural level, along the whole circumference or in vertical extension at any level, with a peak incidence in the fifth decade. No smoking habits correlation has been found. Distant metastases can occur more frequently than in SCC, but often show a very

low growth rate.

This peculiar way of tumour spreading requires a careful attention in frozen section examination of tracheal margins.

Reported 5- and 10-year survival rate is about 65–85% and 40–55%, respectively (7,10,11).

Secondary malignant tracheal involvement may also occur by direct extension from mediastinal tumours, as haematological disorders, neoplasms of other organs like larynx, esophagus, lung, thyroid, or from pathologic cervico-mediastinal lymph nodes invasion; moreover,

Figure 1 Endoscopic view of squamous cell carcinoma.

Figure 2 Endoscopic view of adenoid cystic carcinoma.

trachea may be the site of metastatic diffusion from distant diseases.

Clinical aspects

Dyspnoea, cough, haemoptysis and shortness of breath on effort are very common presenting symptoms, however tracheal tumours may often be underestimate for months or years, especially in case of ACC, mucoepidermoid carcinoma or carcinoid, due to their silent and slow-growing features (12).

They are commonly misdiagnosed as asthma, but when the lumen progressively narrows, patient will develop dyspnoea at rest, hoarseness, wheezing, stridor, revealing an airway obstruction, that may rapidly become a life-threatening condition (13,14).

Other symptoms may be dysphonia from recurrent laryngeal nerve involvement, recurrent pulmonary infections from distal obstruction or dysphagia from esophageal invasion (15).

Diagnostic imaging

Standard chest radiography is often the first imaging study requested in patients with such respiratory symptoms, but signs of tracheal tumours, as obstruction of air column, can be identified in only 18–28% of affected patients (16).

Neck and chest computed tomography (CT) (*Figure 3*) is still the most accurate and useful method to evaluate the intra- and extra-luminal extension of disease, the depth of invasion, the involvement of adjacent organ and pathological lymph nodes, and the presence of distant or local metastasis (17).

Positron emission tomography (PET), as in lung cancer
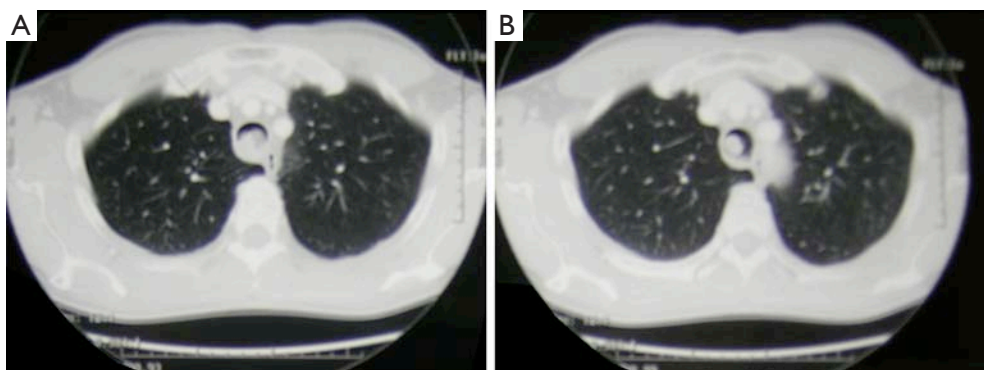
Figure 3 CT presentation of adenoid cystic carcinoma.
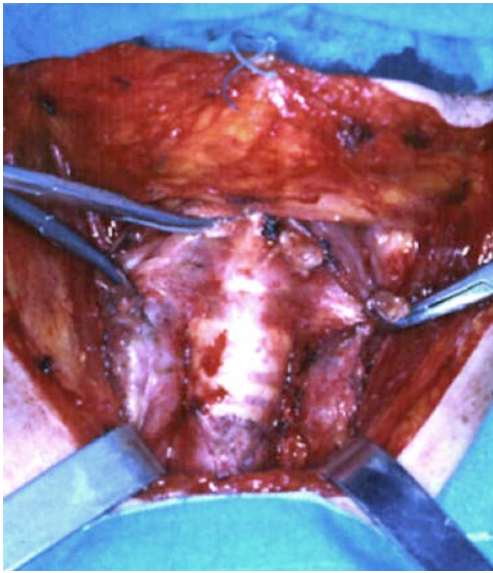
Figure 4 Tracheal view from a cervicotomy approach.

staging, may be helpful to detect local and distant metastasis and to better evaluate the real extension of neoplasm, particularly in SCC, related to its high metabolic activity (17).

Endoscopic evaluation

Tracheo-bronchial evaluation under general anesthesia with rigid and flexible endoscopy is the most useful test in diagnosing and evaluating tracheal neoplasms.

Endoscopy, that should be performed or attended by the first surgeon, allows to carefully evaluate the intraluminal extent of disease, the vocal cords condition, the length of normal trachea and airway diameter, the relationship with cricoid cartilage and carina and to confirm the histologic diagnosis (15,18).

Surgical treatment

Surgical tracheal resection, radiation therapy and endoscopic resection represent the most important treatment options in tracheal tumours, however complete surgical resection is still the best procedure to achieve a long-term survival in selected cases, where no contraindications have come to evidence (14).

Main contraindications to surgery are represented by an excessive length in tumour extension, that would not allow to perform a safe, tension-free anastomosis, presence of distant metastasis and the involvement of surrounding, not

resectable, organs or tissues, severe comorbidities as, for example, active steroid use, not balanced diabetes mellitus or serious nutritional impairment (19).

Surgical approaches and incisions

The choice of way of access represents a fundamental step in surgical planning, where a wrong decision can make the procedure extremely difficult or impossible (20).

Several point should be focused by the surgical team to take the right decision:
- Site and exact extension of the tumour, into and outside of the airway;
- Amount of normal trachea that will remain after the planned resection;
- Age and the body complexion, where an old, kyphotic patient with a short, stiff neck, in whom a resection of no more than 4 cm will be accepted, is a completely different candidate from a young, thin, tall patient, who may undergo up to 6 cm resection (21,22);
- History of previous cervico-thoracic surgery, infection or irradiation.

Upper tracheal tumour

Tumours in the upper portion of trachea will be dealt by a low collar cervical incision (*Figure 4*) with a draped field also for a possible extension along the sternum and right hemithorax.

Middle tracheal tumour

Tumours in the middle portion of trachea will be approached by a combined cervical incision, followed by an upper sternal split (*Figure 5*), with a possible further extension in a full sternotomy (*Figure 6*) or right thoracotomy. This approach will also allow to perform the right, or bilateral, hilar intrapericardial release, while the laryngeal release is rarely needed.

Lower tracheal tumour

Tumours in the lower portion of trachea will be approached through the chest, by a postero-lateral right thoracotomy in 4th intercostal space.

Anterior approach

Low collar incision, with or without partial sternal section, is performed in the standard fashion with patient usually placed in supine position with a folded pillow or an inflatable bag under the shoulders to allow a controlled neck
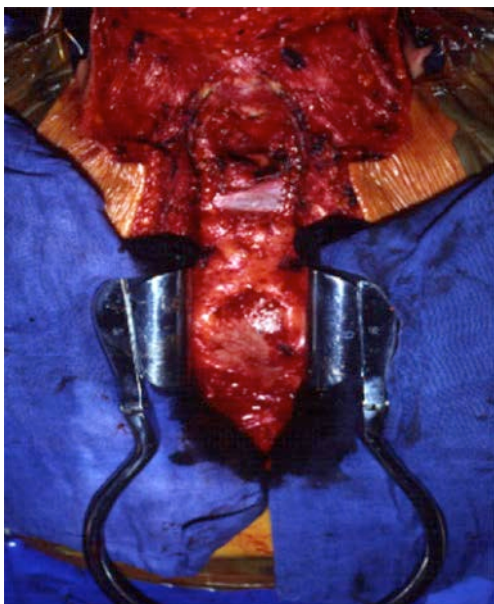
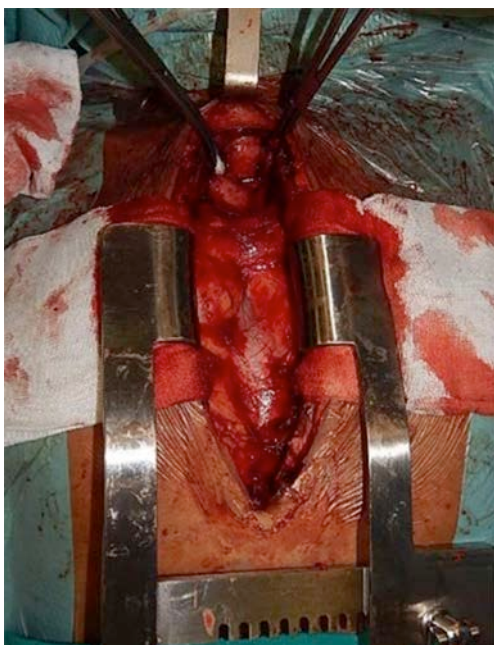**Figure 5** Tracheal view from cervicotomy and sternal split approach.

Figure 6 Sternotomy view.

extension and flexion, that will be needed in the different steps of surgical procedure.

Skin incision, preparation and lifting of muscle-cutaneous flap, initial careful tracheal exposure, protection of recurrent laryngeal nerves, cross-field ventilation and placement of lateral, traction sutures are performed following the standard

criteria used in management of tracheal stenosis (23).

Tracheal dissection is carefully performed with the same attention, but, in neoplastic disease, starting far from the tumour borders, in order to avoid tumour dissemination, to identify the correct surgical planes and to evaluate possible involvement of surrounding organs, as larynx, prethyroid muscles, esophagus or thyroid.

Another important issue is the avoidance of an excessive extension of loco-regional nodal dissection, due to the high risk of disruption of vascular supply of the tracheal wall.

Once the resection is planned, frozen section examination of proximal and distal margins is fundamental, but often, especially in ACC, where the submucosal, longitudinal extension of neoplasm can be found well distant from visible disease, a compromise may be necessary and a microscopical tumour involvement of section margins may be accepted to avoid an excessive tension of the anastomosis.

Also during reconstruction, we perform anastomosis following the Grillo criteria for the anterior wall, using interrupted polyglycolic (Vicryl) 3-0 suture, but with a different technique for membranous wall, where we prefer a running suture with long lasting absorbable 4-0 polydioxanone (PDS) (24).

At the end of the procedure, a thick suture between the chin and the chest (the so-called guardian suture) is passed, to block accidental postoperative neck hyperextension, and left in place for about seven days.

Transthoracic approach

After the right postero-lateral thoracotomy in fourth intercostal space, a complete dissection of middle and lower trachea, esophagus, carina and right pulmonary hilum will be feasible (25).

Intraoperative ventilation, after tracheal section and resection, is conducted by a cross-field armored tube or, as option, with high-frequency jet ventilation, while reconstruction will follow the same steps of anterior approach.

This approach allows to proceed with section of inferior pulmonary ligament and right intrapericardial hilar release, that would increase the mobility of the lower trachea-bronchial structures, reducing the tension on the suture.

As our predilection in every intrathoracic bronchoplastic or anastomotic procedure, like bronchial or tracheo-bronchial sleeve resection or in lung transplantation, a viable tissue flap, in most of the cases a thymic-pericardial fat pad, will be prepared, passed behind the superior vena cava and fixed around the anastomosis, to provide healing factors and to separate the suture from the surroundings vessels.

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Acknowledgements

None.

Footnote

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Reresection for recurrent stenosis after primary tracheal repair

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Abstract: Failure of the anastomosis after primary tracheal reconstruction for benign disease is uncommon. Here we review the available evidence on tracheal restenosis and the results of second reconstructions. Factors associated with failed primary anastomosis are examined. Temporizing immediate and alternative long-term management with T-tube or tracheostomy is described, emphasizing the role of tracheal stenting in abating the urgency for reoperation. From available evidence, elective reoperative treatment of failed tracheal reconstruction should be considered in selected patients after careful review and reversal of patient- and operation-specific factors that initiated failure. Referral to a high-volume center with a deep bench of nursing, anesthesiologic and surgical expertise is recommended for reoperation.

Keywords: Trachea; restenosis; reoperation

Introduction

The reported rate of tracheal restenosis after primary resection and reconstruction for benign tracheal disease is low, occurring in less than 4% of resections at our center (1). The incidence of unreported restenosis, however, may be higher. Treatment of tracheal restenosis involves careful consideration of whether the patient and the operative factors leading to initial failure may be modified. Most failed anastomoses can be temporarily stented with placement of T-tubes. Successful operative treatment of tracheal restenosis may be undertaken in selected patients in a meticulous fashion at high-volume centers.

Definition

Restenosis refers to events during and after primary tracheal reconstruction that lead to either immediate or delayed failure of the anastomosis. Late restenosis with symptoms occurring 3 or more months following operation is very uncommon and may indicate the presence of an underlying systemic disease involving the airway. The causes of early restenosis are limited and accessible to study. A recapitulation of the first operation, the consideration of all potential factors leading to failure and the opportunities to modify them in a future repair should therefore precede a second attempt at reconstruction.

Risk factors predisposing to tracheal restenosis

Any tracheal anastomosis is constructed under tension; the formation of a durable scar, good vascularization of the anastomosed tracheal ends, careful reduction of excessive tension and the absence of excessive anastomotic stress during recovery are all important for a good outcome. In 2014, a review of 94 patients who underwent tracheal resection found that 16% of patients had restenosis (2). At another center of experience, 7.1% of 450 patients had failure of primary tracheal resection and construction (1). For those collecting the experience for publication, the etiology of restenosis is often difficult to determine. Granulations developed in 20% of patients who presented with restenosis (1), but granulations are a phenomenon and not a cause. In patients without granulations (50%), failure

Table 1 Patient factors predictive of failure during tracheal reconstruction (3)

Predictive factors
Delay or lack of healing
Diabetes mellitus
Preoperative steroids
Severe malnutrition
Preoperative radiation
Susceptibility to tension
Immature airway
Thoracic kyphosis
Recurrence of stricture
Connective tissue disease
Persistent inflammation (burn)
Pre-existing infection
Excessive anastomotic stress
Smoking

Table 2 Technical factors predictive of anastomotic failure during tracheal reconstruction

Predictive technical factors
Tension
Insufficient mobilization of the trachea
Long segment (>4 cm) resection
Ischemia
Excessive tracheal dissection
Granuloma formation, foreign body reaction

was likely due to excessive tension and devascularization (1). Patient-specific factors such as diabetes, connective tissue disorders and poor nutrition also contributed to restenosis.

The risk for developing tracheal restenosis may be grouped into factors specific to the patient or to the operation (*Tables 1,2*). Patient-specific factors concern the preoperative use of steroids, for example for airway obstruction; diabetes, as it affects vascularity at the anastomosis; malnutrition, less common as resection for benign disease is usually elective; a young, immature airway; marked kyphosis, creating tension even when the resected airway is short; prior radiation; or, uncommonly, an unrecognized inflammatory or infectious disease.

Operation-specific factors involve the sum of judgments surrounding the conduct of the first operation and include the selection of unsuitable strictures, incomplete mobilization of the trachea or excessive circumferential dissection at

the tracheal margins prepared for anastomosis, causing devascularization; excessive tension at the anastomosis when the stricture was long; and anastomotic inflammation resulting from suture-associated foreign body reaction with formation of granuloma (1,4,5). The latter issue is now mitigated by the use of absorbable braided or monofilament suture. In 2004, a single-institution, retrospective review of 901 patients who underwent tracheal resection found that reoperation, diabetes, long-segment (>4 cm) resection, laryngotracheal resection, age less than 17 years, need for preoperative tracheostomy and need for release maneuvers predicted anastomotic complications (3). In addition, incomplete resection at the time of initial surgery or the presence of tracheomalacia may manifest as tracheal restenosis.

In choosing patients who would benefit from reresection, a critical eye is needed to assess whether risk factors predisposing to tracheal restenosis present at the initial, failed operation can be reversed or modified before another attempt at a resection. The surgeon should note the history of initial presentation and operative details. Candidates suitable for another attempt at resection typically present with short strictures or an avoidable error of judgment during the first operation (*Table 2*). The perioperative care environment must be optimized, and patients likely benefit from undergoing treatment at an experienced, high-volume center.

Evaluation of tracheal restenosis

Patients with tracheal restenosis usually present within 2 weeks after their primary operation (1) with stridor and dyspnea from a narrowed airway. Anastomotic dehiscence may manifest early and dramatically with fever, pain, crepitus and abscess formation.

The history leading to the first operation and prior medications are reviewed. On examination, any airway obstruction, the location of any tracheal stoma and its proximity to the cricoid are noted. Computed tomography is used to assess any extraluminal component to a stenosis and the relation of the innominate artery and other mediastinal structures to the anastomosis.

Bronchoscopy and laryngoscopy are performed to determine the extent of residual normal trachea and the condition of the stricture, the integrity of vocal cords and the presence or absence of tracheomalacia. Performed as a separate procedure prior to operative intervention, endoscopy helps guide the decision to proceed with operative intervention. Key observations include the length of stenosis, the length of both proximal and distal normal trachea,

presence of tracheal mucosa inflammation, and signs of vocal cord impairment. No absolute length of residual trachea indicates the success of another operation; conversely, a short distance of normal trachea may predict the futility of repeat resection. A paretic vocal cord in the medial position indicates damage to one recurrent laryngeal nerve, and the risk reoperation poses to the second nerve must be carefully considered. Avoiding reoperation altogether may be prudent in some patients with overt laryngeal dysfunction lest the remaining recurrent laryngeal nerve suffer damage as well.

Pre-operative management of tracheal restenosis

The surgeon's first priority after failed resection should be to optimize the alternative airway prior to any reresection, so that an ill-fitting tracheostomy or a lack of voice do not create any false urgency for surgeon or patient to "fix the problem" with reresection. Delaying reoperative intervention for a minimum of 4 to 6 months until inflammation subsides is critical to the success of reresection; at our institution, the average time interval between the initial operation to reresection was 8 months (1). Reoperation should also be delayed if infection persists.

Depending on the severity of airway stenosis, in our experience 52% of patients were managed with observation or dilatation before reoperation (1). If the patient remains symptomatic, a T-tube or tracheostomy should be considered. T-tube insertion is our preferred method to optimize the airway as it minimizes inflammation, preserves speech and is easy to manage. The main reason not to use a T-tube is a short distance between the tracheal stoma and the vocal cords, for example after prior laryngotracheal resection, leading to granulations from contact between vocal cords and the upper limb of the tube. A stoma for the T-tube is placed through the prior anastomosis, through the most damaged or stenotic portion of the trachea or at a previously marked, anatomically suitable location in the trachea. If the airway was just dilated during the same procedure, ventilation is maintained through the rigid bronchoscope that is removed once the tube is in place. Some patients with tracheal restenosis may discover that the T-tube is the optimal long-term option. In a series of 140 patients who underwent T-tube placement at our institution, 20% of patients could not tolerate initial T-tube insertion because of obstruction of the upper limb or aspiration (6). However, only 3.6% of patients required tube removal for obstructive problems more than 2 months after placement and long-term intubation of greater than

5 years was achieved in close to 10% of patients (6). About 1 to 2 weeks prior to planned reoperation, the T-tube should be removed and replaced with a tracheostomy to allow the subglottic larynx to recover from irritation caused by the proximal end of the T-tube (6).

The selection of patients for reoperation may be difficult. A "Diagnostic and Therapeutic Main Airway Protocol" was developed in Barcelona, Spain to aid in staging and therapeutic options (7). Stenotic lesions were classified according to stage of development (fibrosis, inflammation/granuloma, malacia, tracheoesophageal fistula), caliber (diameter of stenosis), and length of stenosis (7). This group recommended laser therapy for smaller lesions and resection for larger lesions. In the absence of a preserved cartilaginous airway, we caution that laser therapy of a circumferential cicatricial process affords at best temporary restoration of a functional lumen.

Reoperation for tracheal restenosis

After carefully selecting and preparing a patient for a second resection, the critical determinant of successful reconstruction is a meticulous surgical technique. As for the first operation, the lateral tracheal blood supply must be preserved, extensive anterior tracheal mobilization is provided while protecting the lateral blood supply and excessive anastomotic tension avoided. These steps are particularly important in the reoperative field where the presence of dense scar tissue and limited amount of trachea available for reconstruction decrease the surgeon's margin for error.

The most common approach is an anterior cervical collar incision. About 25% of patients require additional partial upper sternotomy (1). A trans-thoracic approach is selected in the uncommon case of a stricture with carinal proximity. The previous cervical scar and any tracheal stoma are excised.

The sternocleidomastoid muscle is identified. Dissection is performed in the midline and carried down to the surface of the trachea. The dissection should be close to the trachea and midline to avoid impairing the recurrent laryngeal nerve or lacerating the esophagus; circumferential exposure of the trachea is only necessary at the level of the failed anastomosis. The trachea is exposed from cricoid to carina in this fashion. The innominate artery may be incorporated in scar tissue on the anterior tracheal wall; if exposed, the artery should be buttressed with a flap of sternothyroid strap muscle to help prevent formation of tracheoinnominate fistula. At the border between stricture and lower trachea, circumferential dissection is carried immediately on the tracheal wall; any distance taken

from the wall risks injury to the recurrent laryngeal nerves. This part of the dissection must not be hurried.

To address the stenotic trachea, first the trachea distal to the stenosis is opened by an anterior incision. The endotracheal tube is withdrawn and lateral traction sutures are placed in the distal healthy trachea. The distal trachea is intubated with a sterile endotracheal tube and cross-field ventilation is initiated. The stenotic segment is excised; the average resected specimen is 3.5 cm (1); since some or most of this distance represents scar, its removal cannot be equated with loss of tracheal length. Judgment is required to balance complete resection of abnormal trachea with tolerable anastomotic tension. In benign strictures, abnormal trachea may be accepted provided cartilage is stable and luminal diameter acceptable. Strictures after resection for malignancy should accept the margin status found at the time of the first resection.

Our preference is to reconstruct the anastomosis with interrupted 4-0 vicryl sutures; polydioxanone sutures may also be used. Once placed, the sutures are tied with the patient's head in the flexed position. If tension at the anastomosis is excessive, release maneuvers should be performed. About 25% of patients undergoing reresection at our institution required release maneuvers, compared to 6% of patients who underwent primary resection (1).

The most common maneuver to gain additional tracheal length is the Montgomery suprahyoid release (8,9). Useful for cervical reconstruction, the suprahyoid release results in downward displacement of larynx and cervical trachea by 1–2 cm after severing muscular attachments and lateral segments of the central hyoid. This release maneuver often results in temporary postoperative dysphagia. To gain additional length for reconstruction of the lower trachea, intrathoracic tracheal mobilization is performed with division of the pulmonary ligament, release of the pulmonary veins by partial or complete circumcision of the attached pericardium and mobilization of the mainstem bronchi; depending on the type of reconstruction, between 2 and 6 cm of additional tracheal length are generated (10). After wound closure, a heavy suture is placed between chin and presternal skin to prevent extension of the neck during early recovery.

After the operation, the patient is monitored in the intensive care unit. Postoperative bronchoscopy is performed within 7 to 14 days of the operation to evaluate the anastomosis.

Outcomes after reoperation for tracheal restenosis

Donahue and coauthors evaluated outcomes after reoperation for tracheal restenosis and analyzed 75 patients who underwent reoperation from 1965 to 1992 (1). A good or satisfactory outcome was achieved in 91.9% of patients: 78.6% of patients had no physical limitation in activity and good voice and 13.3% of patients had dyspnea on exertion only and adequate voice. Four patients (5.3%) had failed reoperations and were managed with permanent tracheostomy or T-tube. Two patients died (2.7%) from anastomotic dehiscence and mediastinitis. In a series by Jović and coauthors that analyzed 22 patients with recurrent tracheal stenosis who underwent reresection from 2002 to 2010 (11), 95.3% of patients had satisfactory airway lumen with undisturbed breathing. We do not know from these studies the total number of patients evaluated and the proportion of those rejected for reresection.

Another series examined 12 patients who presented with restenosis after tracheal resection from 2000 to 2009 (12). Three patients achieved good outcomes with reresection (two patients underwent dilatation and endobronchial treatments first). The remaining nine patients achieved good results with a combination of dilatations, endobronchial stents, or placement of T-tubes. The circumstances of restenosis therefore seemed to favor non-resectional management.

While the incidence of complications after primary tracheal resection is at least 15%, the risks of reresection are greater. Among the 75 patients who underwent reoperation for tracheal restenosis, Donahue and coauthors found that 39% of patients suffered postoperative complications, anastomotic granulations being most common (15%), followed by retained secretions (5%), wound infection (5%), dysphagia (4%), anastomotic dehiscence (3%), deep venous thrombosis (1%), and pneumopericardium (1%) (1). Complications occurred more frequently in patients who underwent laryngeal release procedures, indicating the deleterious role of tension. Similarly, Jović and coauthors found 31.8% complications among 22 reoperations (11). These included vocal cord immobility, laryngeal edema, granulation, wound infection, wound dehiscence, restenosis, cardiac arrest, and death.

Case examples

The following three cases evaluated and managed by members of the Division of Thoracic Surgery at Massachusetts General Hospital, Boston MA present the range of strictures and outcomes.

Patient 1

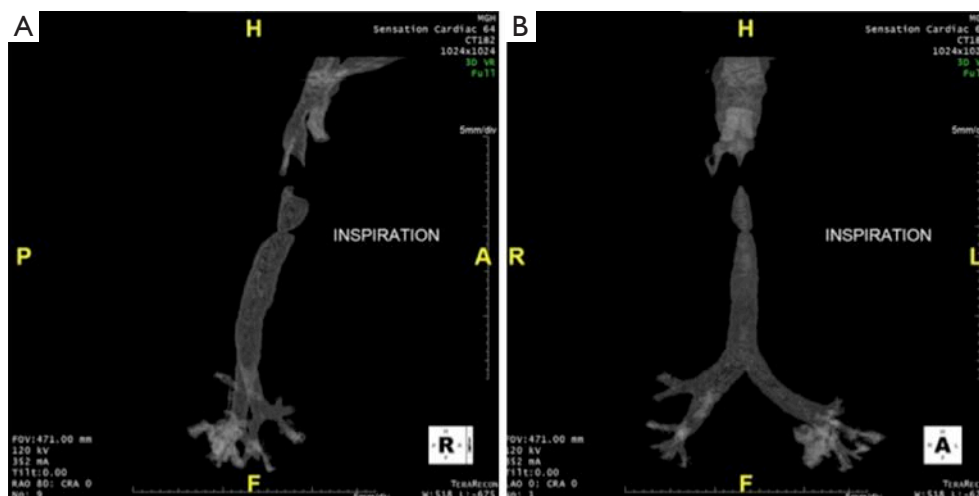This is a 54-year-old man with high tracheostomy for facial

Figure 1 A 54-year-old man with high tracheostomy who developed recurrent tracheal stenosis after primary resection. Preoperative CT reconstruction of the airway demonstrates tracheal stenosis during inspiration in the (A) lateral view and (B) anterior view.
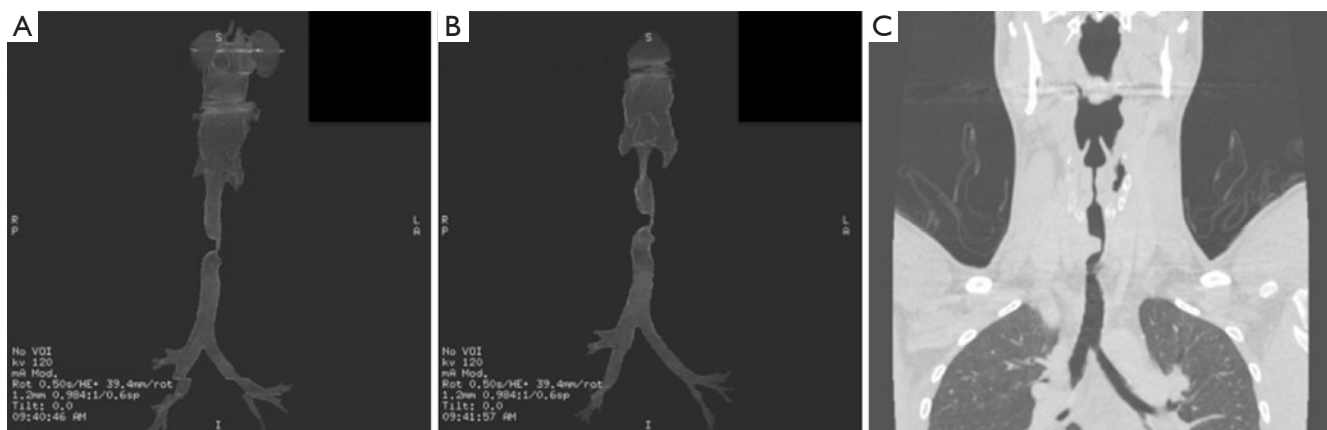

Figure 2 A 22-year-old man with laryngotrachealesophageal cleft who developed tracheal stenosis after primary repair. Preoperative CT of the airway demonstrates tracheal stenosis in (A) reconstructed images during inspiration, (B) reconstructed images during expiration, and (C) coronal view.

injuries. Tracheal stenosis following decannulation recurred after multiple dilations and he underwent a tracheal resection in an outside hospital that failed immediately. The airway was maintained with biweekly dilatations. The first resection failed presumably because a subglottic stricture was not resected. Computed tomography before reresection showed a 1 cm-long high-grade stenosis with a subglottic component (*Figure 1*). During reresection, a scarred anterior cricoid was removed while the posterior subglottic mucosa was intact. Bronchoscopy 1 week after reconstruction demonstrated a widely patent anastomosis. Reresection succeeded because the second operation

removed the subglottic part of the stricture.

Patient 2

This 22-year-old man with Opitz syndrome (manifested by midline defects) underwent repair of a laryngotracheoesophageal cleft as a neonate and a second repair of a subglottic stenosis with cartilage graft at 4 years of age. He presented with noisy breathing and chronic stridor. Computed tomography (*Figure 2*) and bronchoscopy before reresection showed high tracheal bar creating a 1 cm-long stenotic luminal slit 2 mm wide and 1.5 cm deep.

Figure 3 A 30-year-old woman with adenoid cystic carcinoma who developed anastomotic stricture after tracheal resection and reconstruction. Preoperative CT of the airway demonstrates tracheal stenosis in the reconstructed image during inspiration.

Table 3 Approach for successful operative treatment of tracheal restenosis

Approaches
Immediate management
Tracheal dilatation
Temporary airway (tracheostomy or T-tube)
Definitive management
Patient selection
Reversal or control of factors predicting failure (*Table 1*)
Meticulous operative technique (*Table 2*)

He underwent a tracheal reresection through the cricoid cartilage and reconstruction. Bronchoscopy 1 week later demonstrated a widely patent anastomosis. Reresection succeeded because a tracheal bar remaining after cartilage graft reconstruction was removed.

Patient 3

This 30-year-old woman with adenoid cystic carcinoma underwent tracheal resection (6.5 cm) and reconstruction. Four weeks later, she presented with wheezing and stridor. Dilatation failed to improve her stridor. Computed tomography (*Figure 3*) and bronchoscopy before reresection demonstrated a 6-mm stricture at the level of the anastomosis that was 2 cm long. She underwent tracheal

reresection through the previous upper sternotomy and reconstruction. Bronchoscopy 1 week later demonstrated a widely patent anastomosis. Reresection succeeded because the residual stricture was short and reconstruction did not result in excessive tension.

Conclusions

Reoperation for tracheal restenosis after failed primary reconstruction is worthwhile in patients selected for favorable characteristics when performed in an optimal care environment. Neither the true incidence of restenosis nor the precise proportion of patients selected for reresection is known; the former we suspect to be higher than reported, and the latter lower than desirable. One 2012 case report detailing how a patient successfully underwent a third resection and anastomosis of the trachea emphasizes that surgical technique, patient selection and preoperative preparation all play important roles in the success of tracheal reoperation (13). To optimize these factors, surgeons should make liberal use of temporizing measures such as T-tubes or tracheostomy and consider referral to a high-volume center (*Table 3*).

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Reconstruction of the bronchus and pulmonary artery

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Abstract: Bronchovascular reconstructive procedures employed in order to avoid pneumonectomy (PN) in patients functionally unsuitable have provided, over time, excellent results, similar or even better than those obtained by PN. In recent years, new successful techniques have been developed that pertain in particular the prevention of major complications and the reconstruction of the pulmonary artery (PA). Encouraging data from increasing number of published experiences support the choice of parenchymal sparing procedures for lung cancer also in patients with good functional reserve. This is even more true if considering trials published in the last 10 years, thus indicating that improved outcome can be achieved with increased experience in reconstructive techniques and perioperative management. This article discusses the main technical aspects and results of literature.

Keywords: Sleeve lobectomy (SL); pulmonary artery reconstruction; non-small-cell lung cancer

Introduction

Bronchial and vascular sleeve resections have proved to be valid options for the treatment of centrally located lung cancer (1-4). After induction therapy reconstructive procedures may be indicated also when indissociable fibrotic tissue embeds the bronchus and/or the pulmonary artery (PA).

These surgical procedures are employed in order to avoid pneumonectomy (PN) in patients with compromised cardiac and/or pulmonary function.

Although bronchovascular reconstructions associated with lobectomy are surgical procedures with higher technical difficulty if compared with standard major lung resections, postoperative morbidity and mortality data from a number of recent studies report overall better results for patients undergoing sleeve lobectomy (SL) with respect to PN. This is even more true considering trials published in the last 10 years, thus indicating that improved outcome can be achieved with increased experience in reconstructive techniques (5-18) (*Table 1*). These results support the increasing choice of parenchymal sparing procedures for lung cancer also in patients with good functional reserve.

In recent years, new successful techniques have been developed (19,20) that pertain in particular the prevention of major complications and the reconstruction of the PA; these provide good short- and long-term results.

Moreover, many surgeons believe that PN, particularly on the right side, is a disease itself, causing severe postoperative impairment of lung function, cardiac function, and quality of life, and therefore PN should be performed only when necessary to obtain full oncological radicality.

Since the first sleeve resections were reported in the early 1950s (21,22) significant technical advances and increasing experience over time have allowed achievement of excellent clinical and oncologic results, resulting in wide utilization and consensus in the use of parenchymal sparing procedures for lung cancer.

Table 1 Results of main series comparing SL with PN published in the last 10 years: morbidity, mortality, and long-term survival

Authors (year)	Pts		Complications (%)		Mortality (%)		L-recurrence (%)		D-recurrence (%)		5-y survival (%)	
	SL	PN	SL	PN	SL	PN	SL	PN	SL	PN	SL	PN
Bagan *et al.* [2005] (9)	66.0	151.0	28.8	29.9	4.5	12.6	4.5	7.6	–	–	72.5	51.2
Kim *et al.* [2005] (10)	49.0	49.0	7.4	44.0	6.1	4.1	22.0	6.0	22.0	20.0	53.7	59.5
Lausberg *et al.* [2005] (11)	171.0	63.0	0.6*	7.9*	1.7	6.3	36.2	21.3	–	–	45.0	30.4
Ludwig *et al.* [2005] (8)	116.0	194.0	38.0	26.0	4.3	4.6	–	–	–	–	39.0	27.0
Takeda *et al.* [2006] (12)	62.0	110.0	45.0	40.9	4.8	3.6	9.7	10.9	29.0	49.7	54.1	39.2
Parissis *et al.* [2009] (14)	79.0	129.0	16.4	21.6	2.5	8.5	17.7	19.4	–	–	46.8	37.1
Park *et al.* [2010] (15)	105.0	105.0	29.5	33.4	1.0	8.6	14.3	16.2	11.4	21.9	58.4	32.1
Gomez-Caro *et al.* [2011] (16)	55.0	21.0	32.0	33.0	3.6	5.0	3.6	33.0	38.0	71.0	61.0	31.0
Maurizi *et al.* [2013] (17)	39.0#	39.0#	28.2	33.3	0.0	2.6	5.1	2.6	15.4	28.2	64.0	34.5

*, bronchial complications; #, all post-neoadjuvant therapy patients. L-recurrence, local recurrence; D-recurrence, distant recurrence; SL, sleeve lobectomy; PN, pneumonectomy.
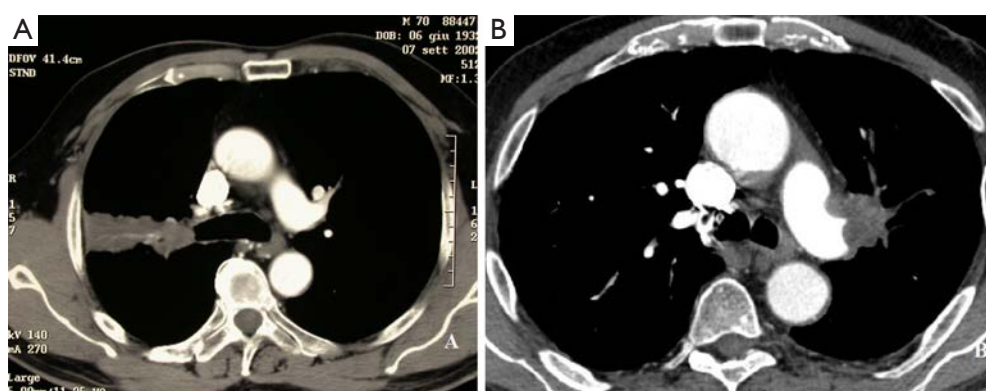
Figure 1 Indication for sleeve lobectomy (SL); computed tomography (CT) scan images. (A) The tumor arises at the origin of the right upper lobar bronchus; (B) the tumor infiltrates both the bronchus and the pulmonary artery (PA) on the left side.

Bronchial resections

Bronchial sleeve for lung cancer is indicated when a tumor infiltrates the origin of a lobar bronchus, but not to the extent that a PN is required. In addition, SL may be indicated for N1 lymph node infiltration of the bronchus and/or the PA, as is often the case in left upper lobe tumors that require combined broncho-vascular reconstruction. Reconstructive procedures also may be indicated after induction therapy when unremovable fibrotic tissue is embedded in the bronchus (*Figure 1*).

Operative technique

Bronchial sleeve resections and reconstructions are commonly performed through the same thoracotomy made for standard pulmonary resections (posterolateral or lateral muscle-sparing incisions, which are both suitable for exposure and dissection) and more recently VATS approaches have been described (23,24). Our technique starts with the dissection beginning in the anterior hilum and then continuing to complete dissection of the main PA. In cases where bulky disease causes increased difficulty during dissection, the pericardium can be opened on either side in order to gain improved proximal control. Next, the main PA is surrounded with surgical umbilical tape. The subsequent steps are specific to the type of sleeve resection performed and each is described independently in the following sections.

Upper SL

On the right side, the dissection starts superiorly at the level of the upper lobe bronchus. The lung is retracted anteriorly, and dissection is continued in the bifurcation between the upper lobe bronchus and the intermediate bronchus. The lymph node frequently found in this location, is elevated away from the bifurcation in order to expose the pulmonary arterial branch to the posterior segment of the lower lobe. Once this branch is identified, the posterior portion of the fissure is completed with a linear stapler. This approach avoids extensive parenchymal dissection in the fissure. The intermediate bronchus is encircled just distal to the right upper lobe take-off, and surgical umbilical tape is placed to aid airway division at the appropriate site. Once complete resectability is confirmed, ligation and division of the pulmonary arterial branches to the upper lobe are performed. Similarly, the pulmonary vein (PV) branch draining the upper lobe is divided with a vascular stapler, taking care to preserve the middle lobe venous drainage. The minor fissure is completed with a linear stapler. The main stem bronchus is encircled with umbilical tape at its origin.

The bronchial resection phase is then started. The main stem bronchus is divided just proximal to the upper lobe take-off. Once the bronchus has been opened, the decision to proceed with a sleeve resection may be made based on macroscopic or microscopic findings. Subsequently, the intermediate bronchus is divided just distal to the right upper lobe take-off. These cuts must be perpendicular to the long axis of the airway.

On the left side, proximal arterial control is obtained taking care to avoid injury to the short apical-posterior segmental branch of the left PA. Dissection is continued along the plane of the artery and the superior segmental branch to the lower lobe is identified. The posterior fissure is then completed with a linear stapler. The arterial segmental branches to the upper lobe are ligated and divided. The upper PV is divided with a vascular stapler. The anterior portion of the fissure is completed with a linear stapler. The main stem bronchus is encircled proximal to the bifurcation, and umbilical tape is placed. The main stem bronchus is divided proximal to the bifurcation, and the left lower lobe bronchus is divided at its origin. The origin of the superior segmental bronchus can be quite close to the origin of the lower lobe bronchus, and the lobar division must leave the bronchus intact without separating the superior segmental bronchus.

A frozen-section examination of the bronchial resection margins is performed in order to confirm the radicality of resection. Microscopic tumors found at the bronchial margin require either additional resection of the involved area or PN.

Different techniques have been described for bronchial anastomotic reconstruction. We favor the use of interrupted sutures of 4/0 monofilament absorbable material (25,26). The employment of continuous running suture (complete or partial) has been described by others (16,27). In our technique, the first suture is placed in an "outside-to-inside" fashion at the junction of the cartilaginous and membranous bronchi. These initial sutures can be immediately tied in order to confer improved stability to this point of the anastomosis. Additional sutures are placed at 2 mm intervals to complete the first half of the cartilaginous anastomosis. Once the midpoint of the cartilaginous bronchus is reached, the anastomosis is then completed on the opposite side of the bronchial circumference in a similar fashion. Sutures are then tied, starting from either end of the cartilaginous portion and working toward the middle. Placing and tying the sutures in this order allows compensation for even large caliber discrepancies. This technique prevents torsion of the bronchial axis and gently stretches and dilates the circumference of the distal bronchus. The anastomosis is then tested with 20 cm water inflation pressure by filling the pleural cavity with saline solution. Needle hole air leaks are usually ignored; however, air leaks between the cut edges of the bronchus, if small, are reinforced with simple interrupted sutures. A large area of leakage may require replacement of the entire anastomosis. Protection of the bronchial anastomosis with a viable tissue flap is recommended by most authors (28,29). The present authors routinely use an intercostal muscle flap (27), which has excellent vascularization provided by the intercostal artery, enables preservation of airtightness even in the event of small anastomotic dehiscence, and minimizes the risk of PA erosion, particularly when an associated vascular reconstruction is performed. Alternatively, the mediastinal fat pad (28), pericardial tissue or pleural tissue (27) has been used as viable flaps. For the final success of bronchial reconstruction, it is essential to avoid tension on the anastomosis. This can be achieved by dividing the pulmonary ligament or, more often on the right side, by opening the pericardium around the PV.

Lower SL ("Y" sleeve)

On the right side sleeve bilobectomy is performed for an endoluminal lesion in the bronchus intermedius that
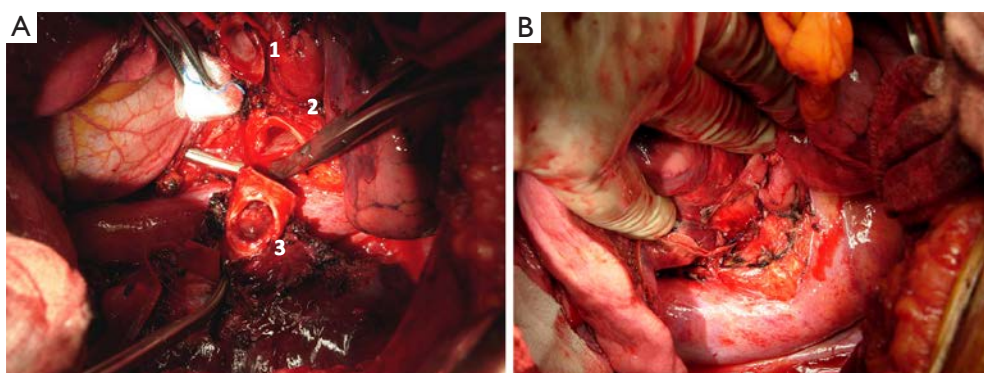
Figure 2 Intraoperative pictures showing left lower sleeve lobectomy (SL) ("Y" sleeve). (A) The bronchi are divided (1, upper lobe bronchial stamp; 2, left main stem bronchial stamp; 3, lower lobe bronchial stamp); (B) completed bronchial anastomosis.

extends up proximal to the upper lobe orifice. The right main stem bronchus is divided at this level just proximal to the right upper lobe take-off and the right upper lobe bronchus is divided at its origin. The upper lobe bronchus is then anastomosed to the main stem bronchus after removal of the middle and lower lobes (the so called "Y" sleeve resection). Due to the reorientation of the upper lobe bronchus after removal of the middle and lower lobes, special care must be taken to avoid torsion of the bronchus at the level of the anastomosis.

For excision of lesions involving the left lower lobe orifice with extension into the main stem bronchus but sparing the upper lobe orifice, a lower lobectomy with sleeve resection of the left main bronchus can be performed. After completion of the bronchial dissection, umbilical tape is passed around the left main stem and left upper lobe bronchus. The left upper lobe bronchus is divided at its origin. Next, the main stem bronchus is divided proximal to the bifurcation and well beyond the extent of the tumor (*Figure 2A*). Once the margins are confirmed microscopically to be negative by frozen-section analysis, anastomotic reconstruction is performed according to the previously described technique (*Figure 2B*). The lingular bronchus may arise proximally to the section line, and care must be taken when dividing the upper lobe bronchus to ensure that it remains intact.

Middle lobe sleeve resection

Middle lobe sleeve resection is performed infrequently. The bronchus to the middle lobe lies immediately posterior to the middle lobe vein. The bronchus is followed back to its origin. A right-angled clamp is placed around the

bronchus intermedius, and this is divided proximally to the middle lobe orifice. The division is slightly angled. The distal division is also angled to preserve the orifice to the superior segment of the lower lobe. The PA lies directly posterior and slightly superior to the bronchus. Therefore, care must be taken to avoid PA injury when dividing the bronchus (*Figure 3A*). The arterial branch to the middle lobe is ligated and divided. After confirmation of negative margins, the airway anastomosis is performed according to the previously described technique (*Figure 3B*).

PA reconstruction

Indication

Primary lung tumors and metastatic N1 lymph nodes with extracapsular extension can infiltrate the PA and involve the right the left main branches to different extents (30).

Moreover, residual tumor or scarring tissue after induction therapy can involve the PA and require a sleeve resection.

In cases of limited, marginal infiltration of the arterial wall, a simple tangential resection with direct suture can be sufficient to achieve a radical exeresis. This technique is generally regarded as a variation of a standard resection and therefore is not considered in this article. In larger defects up to 30% or 40% of the vessel circumference the reconstruction can be performed by a patch (of biological or synthetic material), avoiding a circumferential resection. More extended infiltration requires a sleeve resection and reconstruction by end-to-end anastomosis, or by the interposition of a prosthetic conduit. However, extended infiltration of the PA, such as a left upper lobe tumor infiltrating the concave surface of the PA from its origin down
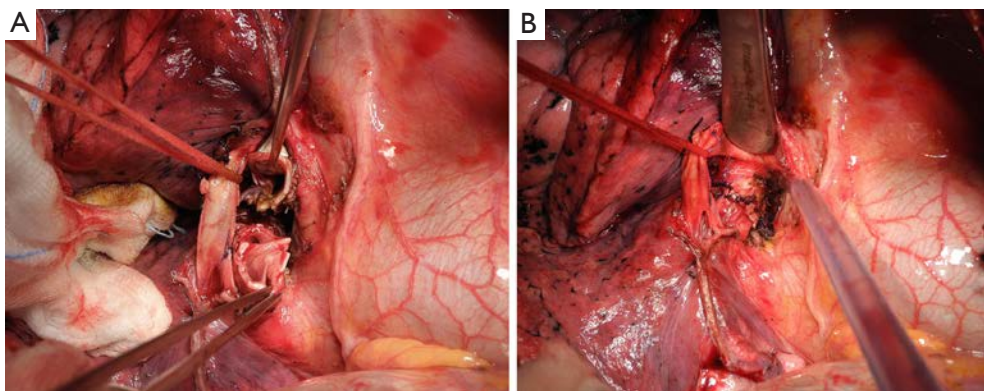
Figure 3 Middle lobe sleeve resection. Intraoperative view. (A) Middle lobe has been removed. The bronchial stamps (the bronchus to the lower lobe and the bronchus intermedius) are visible before anastomotic reconstruction. The pulmonary artery (PA) is encircled with a surgical umbilical tape and retracted; (B) completed bronchial anastomosis.

to the anterobasal artery or, on the right side, posterolateral infiltration from the upper division artery to the artery for the superior segment of the lower lobe, make PN mandatory in order to achieve complete tumor resection.

Operative technique

The first step of the operation consists in achieving full control of the proximal portion of the PA. Although division of the superior PV can facilitate the exposure of the PA, transection of this vessel should be postponed until the feasibility of the procedure has been ascertained.

The resection phase begins once the main and distal PA, the bronchus and both PVs have been duly prepared. The superior PV is generally divided first. Clamping of the proximal PA is then performed after systemic heparinization. In the past we used to clamp the inferior PV to obtain backflow control. Actually, we prefer to clamp the PA distally to the tumor infiltration.

The dose of intravenous heparin represents the only intraoperative management modification adopted by the authors over time. We actually prefer to administer 1,500–2,000 units (about 25 units/kg) instead of a dose between 3,000 and 5,000 units used in the past. Heparin dose has been reduced to prevent postoperative oozing, especially from the lymphadenectomy sites. We have observed that, with progressive reduction of mean clamping time due to increased experience, this dose proves effective in avoiding the risk of thrombosis. Heparin is not reversed by protamine after decamping, once the vascular reconstruction has been completed.

Partial resection and patch reconstruction

Patch reconstruction can be used in a variety of conditions ranging from limited infiltration of the origin of segmental arteries to larger resection of the PA involving less than one half of the vessel circumference. If the infiltration is more extended a sleeve resection with end-to-end anastomosis or conduit interposition has to be performed.

Various materials have been proposed and used for patch reconstruction, including synthetic or biological options. One biological option is represented by the venous patches including azygos, saphenous and superior PV patches. Azygos vein patches present adequate characteristics, but are available only on the right side and provide limited amount of tissue. Conversely, superior PV can provide similar characteristics to the vessel to be reconstructed, but superior PV patch can be generally obtained in case of concomitant left upper lobectomy, since anatomical reasons make its availability more difficult on the right side. When the extra-parenchymal portion of PA is free from tumor, the PV can be closed proximally by a thoraco-abdominal (TA) stapler (30 mm) and is ligated more distally at the extralobar origin of its branches. Then it is sectioned proximally and distally between sutures, so that a 1–2 cm conduit is obtained; a patch adequate for PA reconstruction can be easily obtained trimming the PV conduit.

Among the biological materials, the authors recommend the use of the autologous, bovine or porcine pericardium. In particular, they prefer the autologous pericardium because it has a number of advantages: it shows adequate thickness and resistance, it is cost-free and available on both sides of the chest, and it has superior biocompatibility if compared with
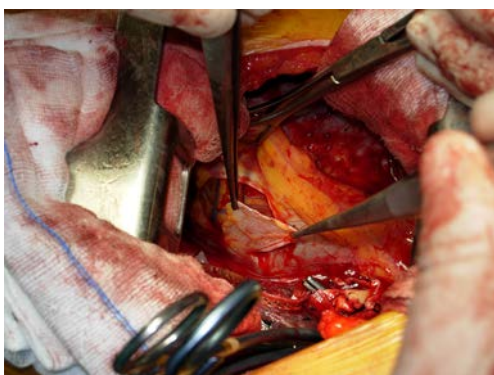
Figure 4 The introperative picture shows the harvesting of the autologous pericardium performed anteriorly to the left phrenic nerve for pulmonary artery (PA) patch reconstruction.

the bovine pericardium. Moreover, it provides an amount of tissue that is sufficient also for large defect repair, and does not require a separate surgical procedure for its harvesting. However, fresh autologous pericardium has some technical limits, since it has a tendency to shrink and curl making more difficult the adaptation and suturing of the patch to the vascular wall.

Bovine pericardium displays limited elasticity and exhibits even and stiff edges that considerably reduce the pitfall of harvesting, trimming and suturing the autologous pericardium.

In order to improve technical features of the autologous pericardium, over the last decade, the authors have devised and employed an intraoperative method of fixation of the patch by a glutaraldehyde-buffered solution (19). The glutaraldehyde preservation of the pericardium minimizes its tendency to retract and curl, thus allowing an easier vascular reconstruction, and reducing the risk of bleeding from the patch suture related to the elastic recoil of the autologous pericardium. Harvesting of the autologous pericardium is performed anteriorly to the phrenic nerve, leaving open the pericardial defect (*Figure 4*).

The patch is appropriately trimmed and secured to the arterial wall by two stay sutures at the opposite sides of the vascular defect. Suturing is done with 5–0 or 6–0 monofilament non-absorbable material proceeding from top-to-bottom "artery first", and then continuing from bottom-to-top "patch first", while the assistant grasps and stretches the patch. The inferior stay suture is not tied: it is used only to keep the patch in place and is removed when the suture line reaches its level.

In patients requiring also a bronchial anastomosis, the PA

patch reconstruction is generally performed first, in order to reduce clamping time.

Check of the suture line after residual lung re-expansion is mandatory, especially if fresh autologous pericardium is used for reconstruction, since retraction of the patch margins may result in bleeding sites when tension changes are applied on the PA axis.

Sleeve resection and reconstruction by end-to-end anastomosis

In patients that require a combined bronchovascular sleeve PA reconstruction is usually performed after completion of the bronchial anastomosis to minimize the manipulation of the vessel.

When transecting the artery, both proximally and distally, regular and even margins are desirable, even at the cost of some loss of tissue. This allows proper placement of the stitches and yields an even inside lumen. In addition, regular suture borders facilitate the correction of the large caliber discrepancy that usually occurs. In addition, the exposure of the bronchial stumps is optimal when the artery is divided. If the vascular and bronchial procedures are done simultaneously, the bronchial axis is shortened, and the PA stumps are opposable with acceptable tension. On completion of the bronchial anastomosis, the distance between the two arterial ends will be markedly decreased, and it can be further reduced by elevating the lower lobe while suturing. Restoration of blood flow and removal of the proximal clamp relieves any residual tension. If the distance between the arterial stumps is deemed excessive, the interposition of a prosthetic conduit is indicated. The anastomosis is performed with running 5–0 or 6–0 monofilament non-absorbable material. Additionally, the sutures are placed very carefully to avoid stenosis. End-to-end anastomosis can be technically difficult due to unexpected traction between the stumps and caliber discrepancy.

Long-segment PA reconstruction

In case of isolated extended PA defects more than 2.5 cm in length it could be indicated a reconstruction by a wide patch or by a prosthetic conduit.

Wide patch reconstruction is indicated for longitudinal defects on one aspect of the PA when the opposite side of the circumference of the vessel is free from tumor (*Figure 5*). If this is not the case, an interposition of a prosthetic conduit is required. Patch reconstruction technique has been previously described. In the following paragraph we

are describing the conduit reconstruction.

Sleeve resection and reconstruction by a prosthetic conduit. In some patients after sleeve resection of the PA an excessive distance between the two vascular stumps may result. This condition could produce an high tension on the anastomosis. Such technical situation may occur, usually on the left side, in those cases requiring resection of a long segment of the PA without associated bronchial sleeve resection, because the lobar bronchus is not involved. In these cases the vascular reconstruction cannot be performed by a direct end-to-end anastomosis and a prosthetic conduit interposition is required.

Although the need for a vascular conduit is not a frequent
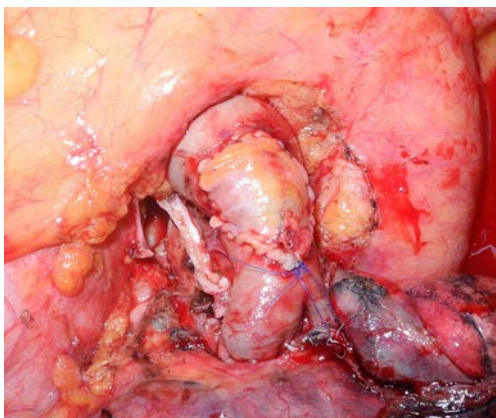
Figure 5 Intraoperative picture illustrating completed long-segment left pulmonary artery (PA) reconstruction by a wide patch of superior pulmonary vein (PV).

condition, various materials and different techniques have been proposed for such reconstructive procedure.

Biological materials are generally preferred because of higher biocompatibility and lower risk of thrombosis. The authors have reported the successful use of the autologous and the bovine pericardium (31). More recently, the current authors have introduced the use of porcine pericardium. Intraoperatively, the pericardial leaflet is trimmed to a rectangular shape and wrapped around a chest tube or a syringe of appropriate diameter and sutured longitudinally. In our initial experience this suture was performed manually with a 6–0 monofilament non-absorbable material. More recently we have described a technical alternative with a mechanical suture using a linear stapler for the conduit construction (*Figure 6*). The creation of a 1–2 cm conduit is so accomplished. When the autologous pericardium is employed the epicardial surface is oriented inside the conduit lumen.

A very interesting alternative for conduit reconstruction is represented by the superior PV of the resected upper lobe when the extra-parenchymal portion of this vessel is free from tumor (20,32). The technique used in order to obtain the PV conduit is the same described in the previous paragraph for PV patch tailoring.

The venous conduit is an ideal substitute for PA replacement since it has adequate thickness and structural similarity with the arterial wall. It is advisable to tailor the length of the biological conduit on the basis of the resected arterial segment, because the elasticity of the two tissues is comparable.
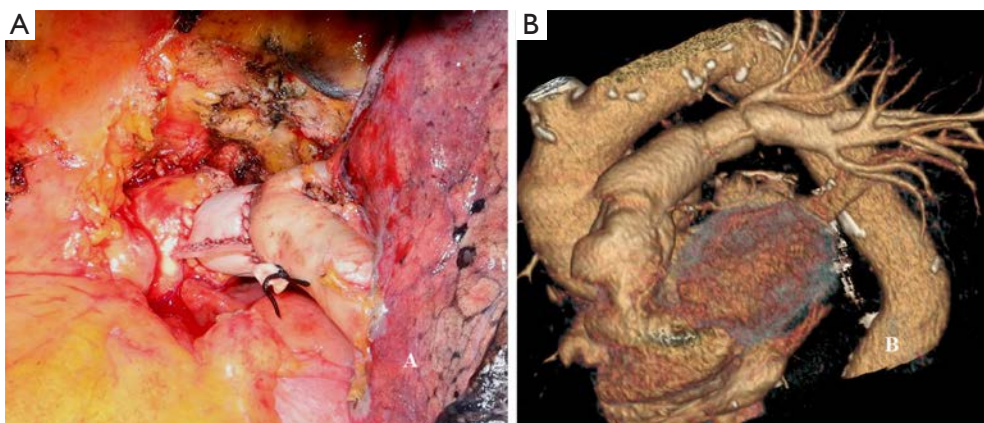
Figure 6 Long-segment pulmonary artery (PA) reconstruction by porcine pericardium conduit. (A) Completed reconstruction of the PA; intraoperative view; (B) computed tomography (CT) with volume rendering showing the complete patency of the reconstructed PA 1 year after surgery; mechanical stapler line between the proximal and distal anastomoses is visible.

The proximal anastomosis is performed first with running 5–0 monofilament suture. The distal anastomosis is then performed with the same technique, after the conduit length has been checked.

Care must be taken to avoid lengthening of the reconstructed PA, which may cause kinking of the vessel, impaired blood flow and therefore thrombus formation.

For the final success of the reconstruction, it is fundamental to avoid tension on the anastomosis. Tension release can be improved by sectioning the inferior pulmonary ligament and, on the right side, by opening the pericardium around the inferior PV.

Technical and perioperative issues

The good final outcome in every parenchymal sparing reconstructive procedure is principally the result of a meticulous surgical technique. However, there are some critical and controversial aspects concerning intraoperative and perioperative management of a bronchial sleeve resection and/or PA reconstruction that are of a different nature and may determine the outcome. In order to take stock of what we have learned from these lung-sparing operations over time, we have analyzed some of the most important aspects independently in this section.

An aspect that still remains controversial is the use of postoperative steroids in patients undergoing bronchial resection. We believe that the postoperative use of low dose steroids is favorable because it reduces secretion retention and atelectasis, facilitates parenchymal reexpansion, and minimizes the risk of dehiscence and granuloma formation. Aerosolized steroids are also part of postoperative treatment.

When considering the role of bronchoscopy in these complex lung-sparing operations, it is important that an endoscopic examination is performed by one of the operating surgeons in candidates for a sleeve resection. This is advantageous at the time of the operation, when the bronchi are incised and divided. It is also useful to have precise knowledge of the preoperative and intraoperative appearance of the airway to detect a stiffness of the bronchial wall that may indicate peribronchial tumor infiltration. This is crucial in areas where the bronchus is known to be adjacent to the PA, which consequently might be involved.

Routine bronchoscopies are performed at the end of the surgical procedure, before discharge from the hospital, and after 1 and 6 months.

Bronchoarterial fistula can be effectively prevented by interposing a viable tissue flap between the two structures. The use of mediastinal fat pad, pericardial flap, or pleural flap has been reported (27,29). However, an intercostal muscle flap is preferable because of its excellent vascularization provided by the intercostal artery (28).

The preparation of the flap is performed before opening the chest, and the rib retractor is not inserted until the procedure is completed to avoid crushing the intercostal vessels. The periosteum of the fifth rib is incised and then separated from the bone in continuity with the underlying intercostal muscle. Care must be taken to preserve the muscular insertion to the periosteum to avoid injuring the intercostal neurovascular bundle. The intercostal muscle is then incised in the vicinity of the underlying sixth rib and the anterior insertion of the flap is divided. The pedicle is ligated at its anterior extremity. When the bronchial anastomosis is completed, a large right-angle clamp is slid between the PA and the bronchus, and the suture at the extremity of the flap is slid backward around the bronchial anastomosis and between the bronchus and the PA. The flap is then twisted until its pleural side is in contact with the bronchial anastomosis and the pleura are secured to the bronchus by interrupted absorbable 4–0 sutures.

A main concern in bronchial and vascular reconstructive procedures is avoiding tension on the anastomosis.

During a PA patch reconstruction procedure, if some degree of tension exists, it is safer to complete the posterior portion of the suture and subsequently parachute the two stumps together while lifting the lower lobe. When a patch reconstruction is associated with a bronchial sleeve, the bronchial axis is shortened, and the length of the artery remains stationary. The PA may tend to kink and fold over on itself. The repositioning of the PA caused by the re-expansion of the lower lobe may increase this risk further. Impairment of blood flow may ensue, and thrombosis may occur. Under these circumstances, it is better to cut away the distorted segment and proceed to an end-to-end anastomosis.

During an end-to-end PA anastomosis reconstruction, dividing the pulmonary ligament or, more often on the right side, opening the pericardium around the PV can be useful to obtain a tension-free suture.

The main pitfall in the use of a prosthetic conduit for PA reconstruction is sizing its length. Application of the proposed technical issues will prevent this problem. The current authors believe that the autologous PV conduit is preferable for PA reconstruction because it is very easy to use and because other materials might increase the

risk of thrombosis. Autologous vein conduit is fresh and unpreserved, cost-free, and biocompatible. Conversely, bovine and porcine pericardial tissue are less cost effective and less biocompatible.

Non-invasive radiologic techniques such as magnetic resonance angiography (MRA) or computed tomography (CT) scan with contrast medium and three-dimensional (3D) volume rendering provide outstanding imaging of the PA and may be very useful in demonstrating patency problems even in the immediate postoperative period. In the absence of clinical symptoms, pulmonary angiograms in addition to perfusion lung scans are redundant. In the long term, CT with contrast medium has proved to be a handy, noninvasive diagnostic tool that is useful to evaluate both PA patency and distal PA branching, as well as the overall oncologic status of the patient.

When PA reconstruction is required, appropriate anticoagulation management is crucial. Initial reports (33) did not clarify this important aspect. Historically, systemic anticoagulation was initiated during operation (3,000 to 5,000 U heparin sodium) (34) and maintained by subcutaneous injection of heparin (15,000 U/day) for 7 to 10 days. We now believe that intravenous injection of 1,500 U heparin sodium during the resection phase without reversal by protamine sulphate at the end of the procedure (27,32), as well as 6,000 U/day low weight molecular heparin administered subcutaneously for 7 days after surgery is sufficient.

Induction therapy

When considering patients with locally advanced non-small cell lung cancer, induction chemotherapy or chemoradiotherapy has become a standardized indication especially in the presence of N2 disease. However, although the beneficial prognostic effects of neoadjuvant therapy have largely been proved, concern about an increased risk of complications when complex reconstructive procedures are performed after oncologic treatment, has limited the diffusion of such operations within multimodality treatment options. Additional risks may be related to the increased difficulty in surgical dissection caused by diffuse fibrotic reaction, and to the potential healing impairment of the reconstructed bronchus caused by tissue damage and compromised vascularization.

After induction treatment, the dissection of the pulmonary hilum and mediastinum can be difficult and hazardous because the bronchial and vascular structures may be embedded in the desmoplastic reaction and scarring tissue produced by the chemotherapy and radiotherapy. Technical expertise and mature surgical judgment are needed, because it is generally in this step of the operation that the tumor can be judged amenable to a sleeve resection or a PN, or considered unresectable. Shrinkage of tumor and fibrosclerotic reaction produced as a consequence of induction therapy usually increase the technical complexity of surgical dissection and may pose doubt in the identification of viable tumor at this site. Frozen-section histology should therefore be performed on all suspicious tissue. However, after chemotherapy or chemoradiotherapy, sleeve resection with reconstructive procedures may also be indicated when indissociable fibrotic tissue with no residual tumor is embedded in the bronchus and/or the PA. In some situations both the upper lobe bronchus and the PA can be encased in fibrotic tissue even without tumor cells at frozen-section analysis. Because lobectomy is technically impossible and PN is the alternative, we think that this is a good indication for a combined bronchovascular reconstruction. In their initial experience the current authors first reported in 1997 the possibility of performing bronchial and arterial sleeve resection after induction chemotherapy with no mortality, no bronchial and vascular complications, and no local recurrence (L-recurrence) in the airway. The overall perioperative morbidity rate in a series of 27 patients was similar to that reported in patients undergoing post induction standard resection in the same period. In addition, 1- and 4-year survival rates (78% and 39%) did not show significant differences from those reported in the standard resection series (65% and 36%) (35,36). These results have subsequently been reproduced and further developed by other investigators worldwide, but available data remain limited, with the largest published series including fewer than 50 patients (37).

In 2013 the authors published the long-term results of their experience comparing SL with PN after induction chemotherapy (17). A total of 39 patients undergoing bronchial and/or vascular reconstruction associated with lobectomy were analyzed and compared with 39 patients undergoing PN over a 14-year period. Postoperative complications occurred in 28.2% of patients receiving bronchovascular reconstruction and in 33.3% of the PN group, without statistically significant difference between the two surgical options. Complications related to the reconstructive procedure occurred in one patient: a late stenosis of the bronchial anastomosis was observed and it

was successfully treated by laser and stenting. Postoperative mortality rate in the PN group was 2.6%, while there was no mortality in the SL group. Difference in postoperative mortality was not significant (P=0.3).

The tumor recurrence rate was 20.5% in the SL group (loco-regional in 2 patients, distant in 6) and 30.8 % in the PN group (loco-regional in 1 patient, distant in 11), but this difference was not significant. In particular there was no significant difference between the two groups if considering loco-regional recurrence rate only (*Table 1*).

Results of surgery

When considering experiences reported in the literature during the last 20 years, the analysis of long-term survival according to stage and nodal status shows that SL results in higher survival rates for stages I and II. The survival advantage in stage III patients appears to be limited (7,11,14), and the role of parenchymal sparing operations in patients with N2 disease still remains undefined (8,38).

Nagayasu and colleagues (18) comparing long-term results of bronchovascular reconstructions performed in two different time periods over 30 years' experience, reported results dramatically influenced by the high rate of pN2 and even pN3 patients treated during the first period, thus indicating the importance of a correct surgical indication when performing reconstructive procedures for lung cancer.

It has been demonstrated (34,39) that the survival of patients undergoing PA reconstruction is comparable, stage-by-stage, to that reported in the major reviews on lung cancer surgery and sleeve resection in the literature. The impact of nodal status on survival is also comparable to that reported for bronchial sleeve and standard resection. Once the decision to resect the disease with intent to cure is taken, PA reconstruction can also be proposed as an adequate procedure in this setting. Moreover, there is no significant difference between PA reconstruction alone and PA reconstruction associated with bronchial sleeve in terms of postoperative mortality and morbidity (40). One apparently new datum that surfaces from our more recent study (39) and is different from our previous report (34) is that combined bronchovascular reconstructions may offer better survival. This suggests that even this complex lung-sparing operations can be pursued with intent to cure as long as a complete anatomic resection is achieved (11,34,39-43).

However, postoperative morbidity and mortality data reveal overall better results for patients undergoing SL with respect to PN (*Table 1*) (5,6,14,15).

An interesting meta-analysis (1) including series published between 1996 and 2006 has compared early and long-term outcome of SL with those of PN. A total of 2,984 patients have been included in this analysis, of which 21% undergoing SL and 79% undergoing PN. Two-hundred-two patients underwent PA resection and reconstruction in association (164 patients) or not (38 patients) with a bronchial sleeve resection.

Morbidity evaluation from eight studies (5,6,8-10, 12,44,45) showed a pooled incidence of 31.3% in the SL group and of 31.6% in the PN group without statistically significant difference. Similar results were observed limiting the analysis to studies reporting a larger experience (more than 50 patients) of SL. The mean postoperative complication rate reported after PA reconstruction was similar (32.4%) to that reported after bronchial SL and PN. Overall postoperative mortality presented a pooled incidence of 3.5% in the SL group and of 5.7% in the PN group, but this difference did not reach statistical significance. However, when considering only studies with larger number (over 50) of SL, mortality rate was significantly lower in the SL group than in the PN group (5-9,11,12,46).

Literature data show that PN patients appear to experience a higher rate of cardiac complications when morbidity is evaluated according to the type of complication, while SL patients show increased pulmonary and airway complications incidence (5,6,8,10,38).

Overall 5-year survival rate from ten studies (6-12,43-45). was 50.3% after SL and 30.6% after PN, showing a statistically significant difference. The median overall survival was 60 months for the SL group and 28 months for the PN group. This result may have been partially influenced by the higher rate of stage III patients included in the PN group in most studies. However, when considering survival according to pathological N status, pooled 1-year and 5-year survival rate of patients with N0 or N1 disease are significantly higher after SL.

The pooled loco-regional recurrence rate from studies considered in this meta-analysis resulted 16.1% in the SL group and 27.8% in the PN group, but this difference did not reach statistical significance. Otherwise, a significantly lower incidence of L-recurrence in favour of SL (SL, 14.5% *vs.* PN, 28.7%) was reported in the studies with larger number of sleeve procedures (6,7,9,12).

The preservation of lung parenchyma has been indicated by some authors as the possible cause of a theoretical increased risk for loco-regional recurrence

after SL. However although in some experiences (38) a higher L-recurrence rate is reported for sleeve resection with advanced nodal status (N2), the few studies (10,38) analyzing risk factors for recurrence, show that the tumor stage and the nodal status are the only negative predictive factors, rather than the type of operation performed.

Literature data also indicate that lung parenchyma sparing improves postoperative quality of life determining a greater cardio-pulmonary reserve, less pulmonary edema and less right ventricular dysfunction due to a lower pulmonary vascular resistance (47). In an interesting paper from Ferguson the Quality Adjusted Years Quoted was 4.37 after SL and 2.48 after PN (29). Another paper from Melloul has retrospectively analysed postoperative FEV1 reporting significantly higher values for patients undergoing SL (13). In a prospective study by Martin-Ucar the reported mean FEV1 loss after parenchymal sparing operations was considerably less than after PN, indicating a strongly significant prognostic advantage for patients undergoing SL.

Conclusions

It is common knowledge that the results of bronchial and PA sleeve resection improved with increasing experience. When these operations are performed with correct indications, accurate and complete preoperative staging in adjunction with careful surgical technique and perioperative management, they may provide functional advantages of standard lobectomy associated with oncological radicality of PN, even after induction therapy. Results of our and other published experiences support these operations also in patients without functional impairment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Airway anastomosis for lung transplantation

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Abstract: Lung transplantation (LT) is the only viable option for a selected group of patients with end stage pulmonary diseases. During the recent years satisfactory results in terms of long-term survival and quality of life have been achieved with improvements in surgical technique, immunosuppression and perioperative management. Since the beginning, the airway anastomosis has been considered crucial and significant efforts have been made to understand the healing process. A number of experimental studies allowed improving the surgical technique by modifying the technique of suturing, the anastomotic protection and type and dose of immunosuppression, reducing the risk of airway complications. Furthermore, a huge progress has been made in the management of such complications. Early diagnosis of bronchial complications and their prompt and correct management are crucial to achieve long-term survival.

Keywords: Lung transplantation (LT); bronchial anastomosis; airway complications

Introduction

Lung transplantation (LT) is currently considered the only viable option for a selected group of patients with end stage pulmonary disease not responding to medical or surgical therapies and with a life expectancy of less than 2 years. The most common indications for LT include four groups of diseases: obstructive, restrictive, septic and vascular; survival varies according to the underlying disorder, with better results for cystic fibrosis and emphysema and worse for idiopathic pulmonary fibrosis. During the last 20 years the technical aspects of the procedure, organ preservation, perioperative management and immunosuppression have been dramatically improved.

Since the early days of LT, healing of the airway anastomosis has been considered the Achilles' heel limiting survival (1-3). A number of experimental studies have been performed to understand the causes of healing impairment and to reduce the risk of catastrophic events related to airway complications (4,5). The development of the bilateral sequential technique with separate bronchial anastomoses has been somehow forced by the high rate of anastomotic tracheal dehiscence (25%) leading to fatal events (6,7) reported for the en-bloc procedure with tracheal anastomosis. Furthermore, LT represents an exception in the transplantation world: in fact, the lung is the only organ in which the arterial systemic blood supply (bronchial arteries) is not routinely restored during the transplant and a network of bronchial circulation around the anastomosis is detectable only after 4 weeks (8). This detail may explain the frailty of the anastomotic site and why different factors including donor management, high—dose steroids administration, immunosuppression therapy, surgical technique and perioperative management can affect its correct healing.

Historical background

The current knowledge of the process of airway healing

after LT is based on experimental studies performed during 1980s by the Toronto Lung Transplant Group on auto-transplanted lungs in dogs. Initially, they focused on the effects of steroids and azathioprine (the only immunosuppressive drugs used at that time) on the breaking strength of bronchial anastomosis; they reported that only steroids were responsible for the impaired healing while azathioprine had no effects (3). The introduction in the clinical practice of cyclosporine A (CSA) allowed to dramatically decrease the rate of airway complications in the same animal model. These data were confirmed at scanning electron microscopy, showing normal collagen formation at the anastomotic site in animals receiving CSA (4). These studies contributed to reduce the use of steroids before and after LT to avoid impairing of the healing process. However, further studies demonstrated that the administration of steroids plays an important role to prevent rejection and, at ameliorate the patency of microcirculation in case of reperfusion injury (9,10). Low dose steroids also contribute to improve healing of the anastomosis in a non-transplant setting (11). For these reasons they are still included in the immunosuppressive regimen. However, their dose should be reduced as much as possible before the transplant (12).

The effects of the interruption of the bronchial circulation have long been debated. Early studies performed in 1960s showed that if the bronchial vessels are not anastomosed a higher rate of bronchial complications is observed (13,14). However, subsequent studies showed that a fine network of bronchial circulation is detectable starting from the fourth week (8) and that an early network of vessels surrounding the anastomosis is already present after 12–14 days (15). This data confirms previous reports stressing that the first two postoperative weeks are crucial to prevent airway complications (16). Based on these reports, the Toronto Group proposed to buttress the anastomosis with an omental pedicle flap to reduce the early ischemic time and enhance the microcirculation (17,18). They demonstrated that with such technique, after 4 days a network of multiple capillaries originating from the omentum surrounds the bronchus and supports healing. Although this technique has initially met a large consensus, it has been progressively abandoned in favor of new and technically easier strategies to wrap the anastomosis as the use of the intercostal muscle (19,20) or the peribronchial tissue (21).

Evolution of technical details

Since bronchial anastomosis complications can be

catastrophic and significantly affect outcome, the technical aspects of suturing have been repeatedly modified and simplified since the early days. The bronchial anastomosis was initially performed after the vascular anastomoses due to the lateral decubitus of the patient on the operatory table; the cartilaginous portion was completed first with interrupted absorbable sutures, followed by the membranous portion. At the end, the omentum was transposed in the chest and wrapped around the suture line (22). The supine position on the operatory table forced to perform the bronchial anastomosis first, starting from the membranous portion.

Due to the peculiarity of the airway vascular support (low pressure circulation from the pulmonary arteries and systemic pressure circulation from bronchial arteries; both divided at time of transplantation), the length of the donor bronchus has been historically considered crucial to prevent airway complications. The donor bronchus is usually transected no more than one or two rings above the lobar carina to minimize the area of ischemia (23). More recently, several reports suggested that an even shorter length of donor bronchus (close to the lobar carina) might further reduce bronchial ischemia (24-26). This modification significantly contributed to decrease the rate of airway complications, independently from the surgical technique used to perform the anastomosis. However, the excessive shortness of the donor bronchus could create problems to treat major complications in case they occur; in fact, in such situation, mechanical dilation or stent placement might be difficult and sleeve lobectomy or redo transplantation might become the only available options (25).

Bronchial artery revascularization with microsurgery techniques has been proposed to improve healing (27). Although this approach allows full restoration of the bronchial circulation, the technical difficulty and the additional operative time have limited worldwide spreading.

The surgical technique for bronchial anastomosis has been repeatedly modified and even now there are differences between centers. Even the type of suture material is still debated (absorbable *vs.* non-absorbable). The classic technique proposed by the Toronto group was an end-to-end anastomosis with an absorbable 4/0 running suture on the membranous part and single or figure-of-eight stiches for cartilaginous wall (23). Briefly, a silk traction suture or an Ellis clamp is placed at the midpoint of the cartilaginous portion of the recipient airway to retract the bronchus from the mediastinum. The first step is to approximate the donor and recipient posterior peribronchial tissue

followed by a running suture of the membranous portion. The cartilaginous part is sutured with single or figure-of eight stitches, progressively adjusting the mismatch between the stumps and the silk stitch is removed. After completion of the anastomosis, the suture on the posterior peribronchial tissue is continued anteriorly covering the bronchus. This approach has represented, and still represents at several transplant centers, the gold standard. However, some limitations compared to a complete running suture (membranous plus cartilaginous portions) as more time required to perform it, and inflammation caused by multiple stitches that may potentially affect the correct healing have been reported (28,29). For these reasons some authors prefer an end-to-end running technique with an absorbable 4/0 monofilament suture. Although coverage of the anastomosis is usually considered mandatory, at some centers it is not performed at all (Vienna Lung Transplant Center), with equally good results (28). The rate of airway complications is similar with either technique (*Table 1*); furthermore both of them allow easily overcoming of the potential size mismatch between donor and recipient airway.

Telescoping anastomosis with the intussusception of the donor bronchus into the recipient airway has gained widespread consensus in the 1990s to solve the problem of size mismatch and to improve the tightness of anastomosis (30,31); only the cartilaginous part of the bronchus is intussuscepted. However, due to the higher incidence of anastomotic complications, this technique has progressively been relegated to those cases with a natural tendency towards intussusception (28,32).

The technique of bronchial anastomosis in case of pediatric or lobar transplantation (cadaveric or living related) is similar, although the size of the suture is smaller (5/0). In case of living related lobar transplantation, the dissection of the donor bronchus should be minimized to preserve backward blood supply. On right side, the middle lobe bronchus is identified and the incision goes obliquely from above the superior segment bronchus of the lower lobe to just below the middle lobe bronchus; on left side the lower lobe bronchus is transected tangentially above the superior segment of the lower lobe (33).

Risk factors for airway complications after LT

Several risk factors have been considered in the development of airway complications after LT: ischemia, impaired organ preservation, rejection and infection. Prolonged mechanical ventilation of both donor and recipient has been considered to play a role with different mechanisms: by causing a persistent inflammation status and an higher risk of infection in the donor and by determining a barotrauma on the anastomosis in the recipient; furthermore the need of prolonged mechanical ventilation after LT may be a sign of graft failure as a result of prolonged ischemia (25,34). Thus, patients should be extubated as soon as possible (35)

Adequate organ preservation is crucial. The use of low potassium dextrane solutions associated to the administration of prostaglandins to increase the microcirculation flow (36) and the association of retrograde perfusion (37) have contributed to decreased the rate of airway complications; furthermore, limiting the cold ischemic time within 6-8 hours should minimize the risk of injury (38).

Acute rejection has been identified as an independent risk factor for airway complications by causing acute inflammation, submucosal edema and increased vascular resistance with subsequent reduction of graft perfusion (36). Administration of low dose steroids may ameliorate the microcirculation by reducing edema with improvement of perfusion at the anastomotic site; thus, optimizing immunosuppression is crucial.

A strong association between airway complications and Aspergillus infection has been reported (39). Fungal infections are relatively frequent in transplant patients (40). The simultaneous presence of anastomotic necrosis and Aspergillus is correlated with a higher risk of late bronchial complications compared to the presence of necrosis alone. Broncho-arterial fistula has also been reported. An aggressive antifungal therapy should be immediately started even in asymptomatic patients.

Bronchial complications

The incidence of bronchial complications ranges between 7% and 18% with a mortality between 2% and 5% (24,34,41). Early and late complications include bleeding, necrosis, dehiscence, granulations, stenosis and malacia (42). Although several classifications of bronchial healing have been proposed, none has been worldwide accepted. The Couraud grading system based on bronchoscopic surveillance at the 15th postoperative day is well known and it seems to show a correlation with the subsequent onset of airway complications (43). Anastomotic healing is classified as follows:

Grade 1: complete circumferential primary mucosal healing;

Grade 2A: complete circumferential primary healing of

Table 1 Incidence of airway complications after lung transplantation based on the type of bronchial anastomosis

Authors	Year	Type of suture	% of AC
Date	1995	End-to-end interrupted	9.5
Kshettry	1997	Telescoping running[#]	12.4
Herrera	2001	End-to-end running[#]	23.8
Aigner	2003	End-to-end running	2.6
Van De Wauwer	2007	Telescoping interrupted	41.1
Van De Wauwer	2007	End-to-end*	15.7
Weder	2009	End-to-end interrupted	4.9
Van Berkel	2011	End-to-end running standard	8.2
Van Berkel	2011	End-to-end running modified	2.1
Fitzsullivan	2011	End-to-end interrupted standard	18.1
Fitzsullivan	2011	End-to-end interrupted modified	2.3

AC airway complications. [#], nonabsorbable suture; *mixed series with 276 interrupted suture and 28 running suture.
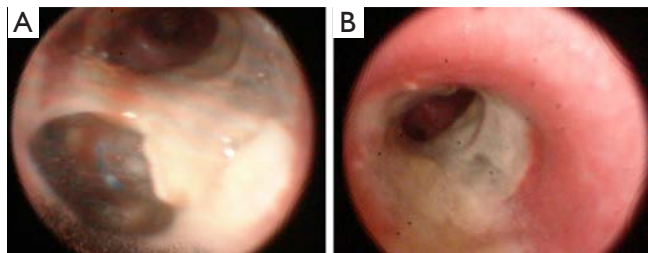
Figure 1 A dehiscence of the bronchial anastomosis can be successfully repaired by careful endoscopic application of fibrin glue. (A) Bronchoscopic view of an anastomotic dehiscence; (B) the dehiscence has been successfully treated with fibrin glue.

the airway wall without necrosis and with partial primary mucosal healing;

Grade 2B: complete circumferential primary healing of the airway wall without necrosis but with no primary mucosal healing;

Grade 3A: limited focal necrosis (extending less than 5 mm from the anastomotic line);

Grade 3B: extensive necrosis.

The development of anastomotic necrosis and dehiscence is related to an ischemic injury and the severity of this complication goes from a focal superficial lesion to extensive necrosis of the bronchial wall that may determine catastrophic consequences with high mortality. These events can be detected in asymptomatic patients during bronchoscopic surveillance or they can be highlighted with radiological studies (computed tomography with multiplanar reconstructions) in patients showing clinical manifestations like fever, cough, dyspnea, prolonged air leaks, pneumothorax, pneumomediastinum with subcutaneous emphysema and mediastinitis with sepsis. When healing, these complications may lead to granulation, stenosis or bronchomalacia. Treatment is based on the severity of the problem, ranging from a conservative approach or minimally invasive treatment for mild lesions to more aggressive therapeutic options including reconstructive surgery, pneumonectomy or retransplantation. In case of a very limited and asymptomatic dehiscence a "wait and see policy" with continuous bronchoscopic surveillance and bronchial debridement can be the first approach; the instillation of glues or sealants has been often reported (44) (*Figure 1*). Stent placement (silicone or covered expandable metallic) is the following step. However, in difficult cases, surgery may be required: direct suture, sleeve resection, pneumonectomy and re- transplantation have been reported, although they carry significant morbidity and mortality (45).

The onset of granuloma usually requires mechanical debridement or laser ablation (46,47). Prevention of recurrence, occurring in 10–50% of cases, includes injection of Anti-fibroblast and anti-inflammatory agents in the bronchial wall to avoid fibroblast proliferation and formation of granulation tissue. Although several drugs have been used, the results are still controversial and the exact dose is not well established yet (47).

The most frequent bronchial complication following LT is stenosis occurring either at the level of the anastomosis or more distally. It is usually related to ischemia and

impaired local microcirculation; however, a diffuse peripheral stricture might be a manifestation of cellular rejection. Patients with bronchial stenosis can be absolutely asymptomatic or present with dyspnea, cough and recurrent pulmonary infections; pulmonary function tests (PFTs) may show a reduction in the forced expiratory volume in 1 second (FEV$_1$). Treatment includes mechanical dilation with the rigid bronchoscope or other instruments (48), balloon bronchoplasty and stenting. The choice of the stent should be evaluated on a case-by-case basis. Silicone stents are usually easy to deploy, they can be removed even after a long period of time and the cost is low; however, there are some disadvantages including the need of constant nebulization to promote airway clearance and the challenging placement in case of a tortuous airway. In this case the use of metallic stents might be helpful (49); however, the complications related to these devices are formation of granulation tissue, airway rupture due to erosion and extreme difficulty in case removal is required.

Malacia is a condition in which the airway tends to collapse during breathing or with cough and it is generally due to ischemia, infection or altered response of the bronchial wall to immunosuppression. Symptoms are dyspnea and stridor mostly evident during exercise, cough and wheezing; PFTs show a marked reduction of all dynamic volumes [FEV$_1$, forced expiratory flow of 25% to 75% (FEF$_{25-75}$) and peak expiratory flow (PEF)]; bronchoscopy allows to confirm the diagnosis. Stenting is usually required.

Overall, early diagnosis of bronchial complications and their correct management are crucial to achieve satisfactory results and a better survival after LT.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

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Idiopathic laryngotracheal stenosis

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Abstract: Idiopathic laryngotracheal stenosis (ILTS) is a rare inflammatory disease of unknown etiology. Infectious, traumatic and immunologic processes must first be excluded. The majority of patients affected are female who present with progressive symptoms of upper airway obstruction, which can extend over a number of years. ILTS is characterized by short segment, circumferential stenotic lesions, located particularly at the level of the cricoid. Bronchoscopic evaluation is essential for establishing the diagnosis and operative planning. Various temporizing interventions have historically been utilized, including dilation and laser ablation, for symptomatic management. However these interventions have demonstrated diminishing returns and poor long-term outcomes. Patients with ILTS should be considered early for definitive surgical intervention to minimize complications and optimize outcomes. Laryngotracheal resection and reconstruction is a viable intervention, which has demonstrated good long-term results and low recurrence rates for this patient population.

Keywords: Trachea; larynx; stenosis; idiopathic

Introduction

Idiopathic laryngotracheal stenosis (ILTS) is a rare inflammatory disease. The first three patients reported in the literature were described by Brandenburg in 1972 (1). There have since been more case reports and series describing this condition, the pathology, management and long term outcomes regarding conservative and definitive surgical intervention. Importantly, it is thought of as a diagnosis of exclusion given after other immunologic, infectious or traumatic etiologies have been excluded. A recent body of research focuses on hormonal factors influencing the development of this disease given the predominance of females affected, however there have yet to be any new causal links identified and the etiology remains unknown (2).

Pathophysiology

ILTS is characterized by the percent of luminal stenosis, the distance of involved airway from the vocal cords, and the overall length of the stenotic segment. Idiopathic disease characteristically is comprised of circumferential lesions of varying length from 1–3 cm, the majority of which demonstrate maximal stenosis at the level of the cricoid (3). On pathologic examination, affected tissue demonstrates replacement of the tracheal lamina propria with dense keloidal, collagenous fibrosis which characterizes the stenotic segment (4). This disease entity is termed idiopathic given the etiology of pathologic transformation remains elusive.

Presentation

Nearly every case study in the literature, including the largest series of patients reported by Wang *et al.*, describes greater than 98% of patients with idiopathic disease being females, with a median age of afflicted patients being 47 years old (5). Clinical presentation includes symptoms of upper airway obstruction including progressive dyspnea on exertion, wheezing, or stridor. Thirty-seven percent of patients report abnormality in their voice upon presentation (5).

Patients typically become symptomatic when their airway is reduced by more than 50% (2). After infectious, neoplastic, immunologic or traumatic etiologies are ruled out, a diagnosis of idiopathic disease is given, which guides initial management. Exclusion of Wegener's granulomatosis is confirmed by a negative ANCA. Patients should be screened for connective tissue disorders by ANA status. It can be elevated without specific diagnosis.

Historically, many patients have undergone conservative medical and endoluminal therapies with reasonable short-term results. These include laser ablation, mechanical dilation using rigid bronchoscopy, or balloon dilatation with flexible bronchoscopy (6). Medical treatment with agents such as mitomycin C (MMC) and steroids are used as adjunctive treatments. However, the rate of recurrence with these therapies has been reported as high as 87% at 5 years (3). Wang *et al.* recommends based on their experience, at most 3 dilations, before referral for surgical intervention, as these interventions may cause further airway damage without long-term improvement. Collectively, these measures are all palliative and temporizing, with diminishing returns, as surgical intervention must be considered.

Pre-operative evaluation

Preoperative planning and evaluation includes appropriate exclusion of underlying immunologic processes, in addition to antecedent events, such as infection, trauma, or prior irradiation. Simple soft tissue X-rays and thin slice spiral CT imaging are used to better characterize the stenotic segments of the airway (*Figure 1*) (5). It is preferred to electively defer surgical management 2–3 months in the setting of active inflammation and perform dilations prior to resection, however, this is not uniformly practiced. Wang *et al.* reports 20% of patients were dilated only at initial evaluation and surgical correction deferred.

All surgical candidates should undergo bronchoscopic evaluation of the airway to identify proximal and distal extent of involvement, as well as degree of active inflammation (*Figure 2*) (5). If the stenosis abuts the vocal cords, or vocal cord mobility is impaired, a single stage repair may not be possible (2). Otolaryngologists should be consulted prior to operative intervention in these patients so as to optimize the ability to extubate the patient post operatively. However, significant stenosis that begins within 5 mm of the glottis is challenging and conditions must be optimal. In those patients deferred because of inflammation, we recommend saline nebulizers twice per day to clear the

inflammatory exudate.

Operative management

ILTS has become an increasingly common indication for laryngotracheal resection in our institution over the past 25 years (2). Definitive resection can be most often optimally achieved via a single stage repair, with or without a posterior tracheal membranous wall flap. Close collaboration with an excellent anesthesia team proves to be the most important intraoperative variable to successful outcomes (2). Extubation at the completion of the surgery is sought and should be achieved in nearly all patients.

Careful endoscopic examination of the airway and identification of extent of diseased trachea is essential. Given the proximity to the subglottic airway and vocal cords in idiopathic disease, most require resection of the anterior half of the cricoid and reinforcement of the posterior cricoid (*Figure 3*) (8). Excessive anastomotic tension and preservation of the blood supply are vitally important. The first two tracheal rings are typically part of the resection, falling approximately 2 cm below the cricoid (9). One must be careful to ensure that circumferential dissection is maintained at the level of the diseased trachea, as tracheal vasculature is segmental and enters laterally (2). Dissection is kept on the trachea at all times to avoid injury to the recurrent nerves.

Most commonly observed with ILTS disease, residual scar will remain on the posterior cricoid plate, given its characteristic circumferential disease pattern. This should be resected and resurfaced with a tracheal membranous wall flap (*Figure 4*) (2). One is able to enlarge the lateral dimensions of the subglottic airway by approximately 4 to 5 mm by meticulously excising small segments of thickened cricoid cartilage on either side and resection of the thickened submucosal scar, while careful to maintain the cricoid structural integrity (7). The mucosa overlying the resected cartilage is importantly preserved and resurfaced as a pedicled flap (*Figure 5*) (8). A single 5-0 Vicryl suture is used to advance the flap and secure it to the cricoid. Previously multiple sutures were used. The anastomotic sutures now are used to secure the flap to the cricoid. This is done to prevent exposed cartilage in the airway and minimize granulation tissue formation.

Once reconstruction commences, reduction of anastomotic tension is important. Interrupted sutures are placed between the inferior aspects of the posterior cricoid cartilage and the membranous wall flap (8). The
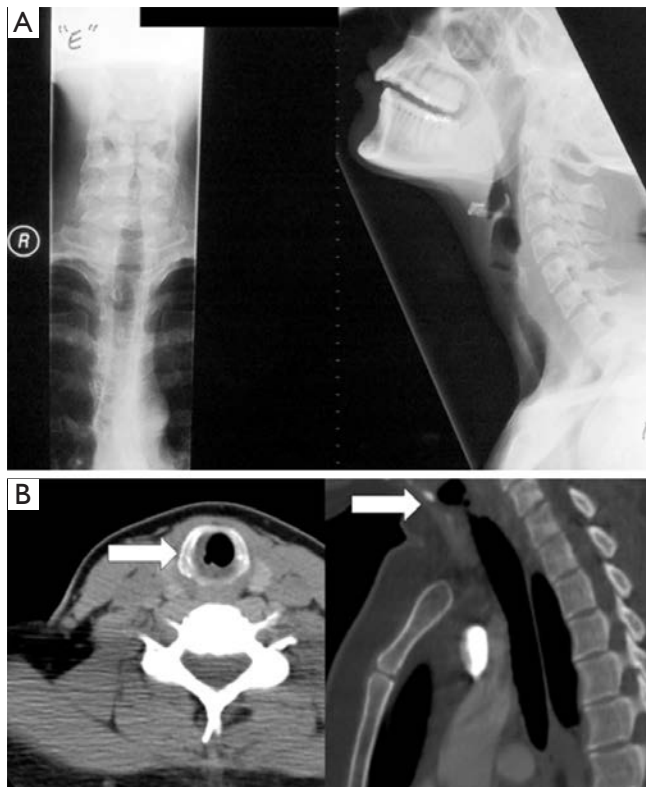
Figure 1 Radiographic evaluation. (A) Simple posteroanterior, and lateral soft tissue radiographs of the neck; (B) axial view (left) and sagittal view (right) of the neck and airway. The arrows indicate the area of stenosis (5).
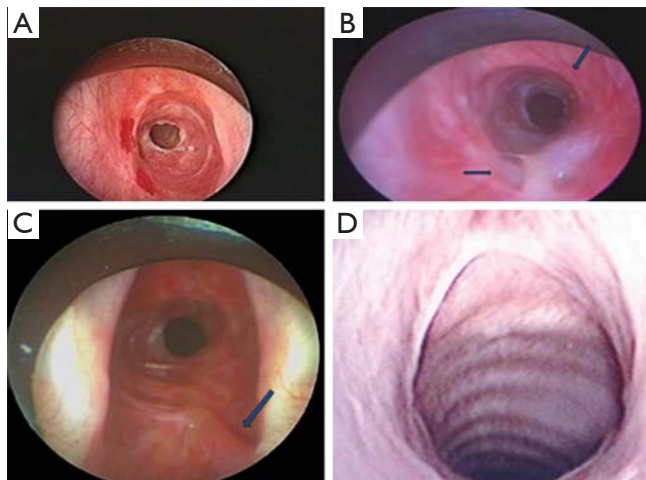

Figure 2 Bronchoscopic evaluation. (A) View of stenosis involving cricoid; (B) stenosis involving cricoid (thick arrow) and posterior cricoid mucosa (thin arrow); (C) fibrous band (arrow) extending to base of right vocal cord; (D) postoperative result. (5).
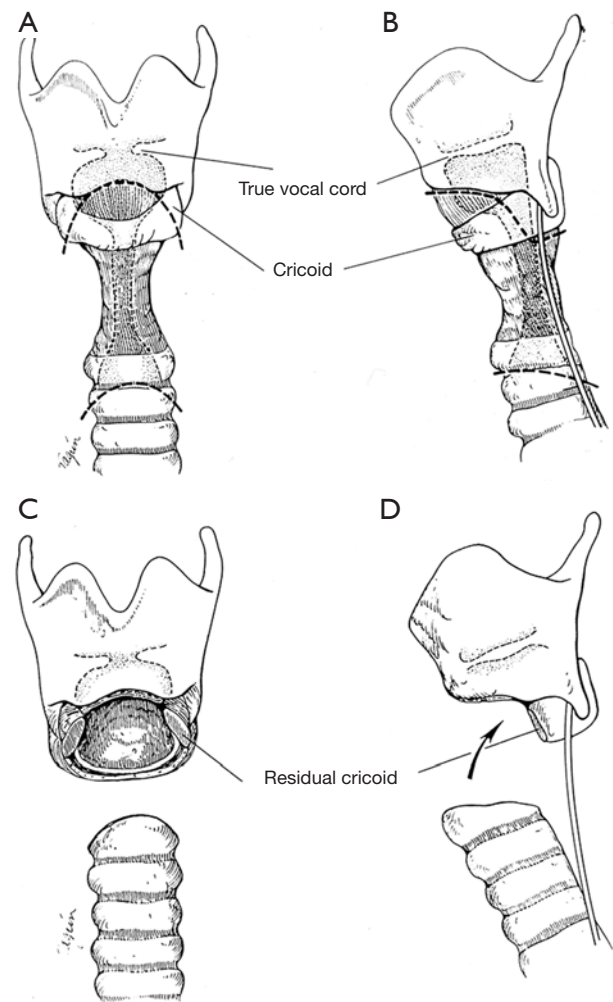

Figure 3 Anterior cricoid plate is removed. Division of larynx and trachea demonstrated by dashed lines (7).

membranous wall flap sutures are placed as vertical mattress sutures so as to have the knots end up outside the lumen of the airway. The laryngeal mucosa is then sutured to the membranous wall flap (2). These sutures can be placed so knots are inside or outside the lumen. Next, working posterior to anterior, the anastomotic sutures approximating the laryngeal mucosa and lateral cricoid lamina sutures are placed first, followed by the tracheal mucosa and cartilage (*Figure 6*) (7).

All sutures are placed first prior to tying down each throw. The traction sutures are then tied down first, followed by the posterior membranous flap and inferior edge of the posterior cricoid plate, followed by the sutures of the laryngeal mucosa and membranous wall flap (2).
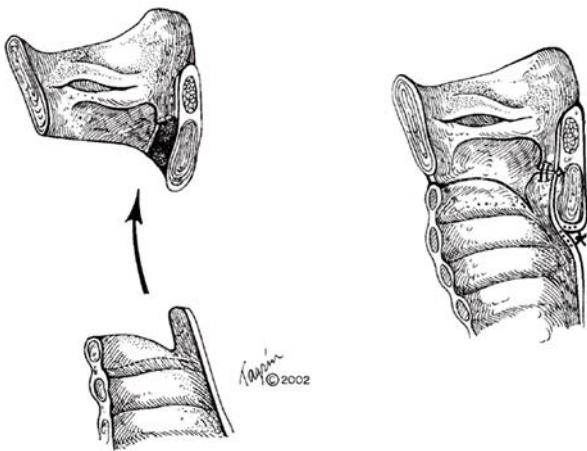
Figure 4 If posterior scarring of the submucosa is present, as typically seen in ILTS, the mucosa and submucosa are sharply dissected off the posterior cricoid plate, leaving the cartilage in situ. A posterior membranous wall flap is then tailored on the distal trachea for resurfacing of the posterior cricoid plate (7).
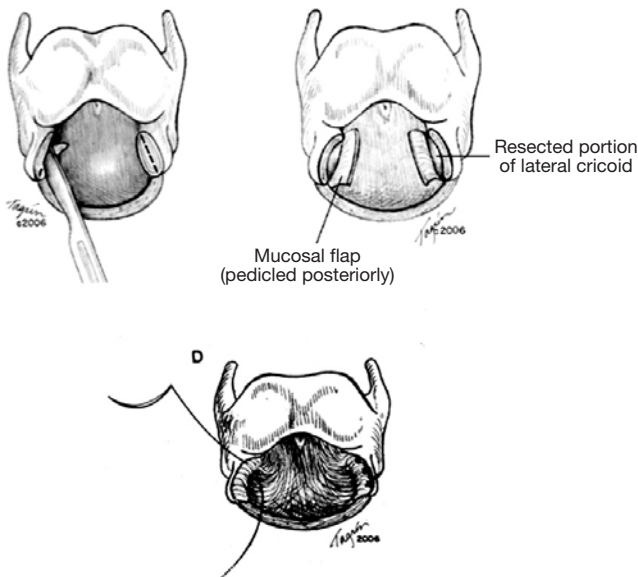
Figure 5 Sharp resection of thickened submucosal tissue is performed laterally. The mucosa must be preserved for subsequent resurfacing. Mucosa overlying resected cartilage is preserved as a pedicled flap. Exposed cricoid cartilage is resurfaced by advancing the mucosa as advancement flap over cricoid and secured with a single interrupted 5-0 Vicryl suture (7).
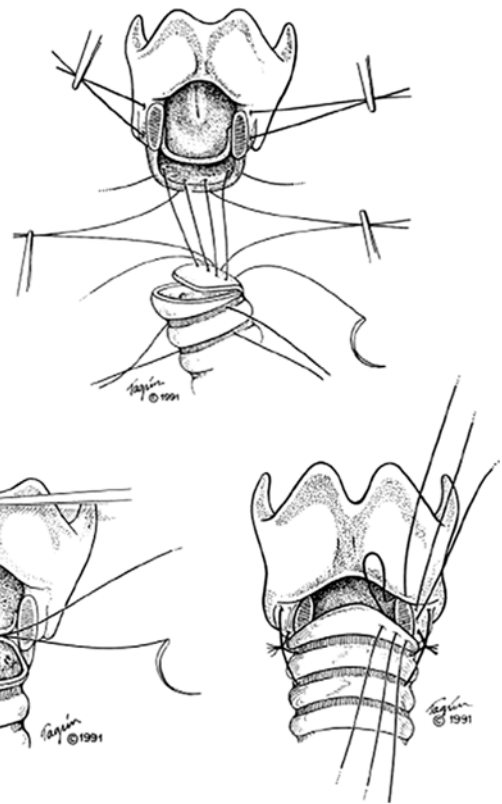
Figure 6 Anastomotic technique. Interrupted sutures between the inferior edge of the posterior cricoid and tracheal membranous wall flap. The sutures should be placed first through the inferior edge of the posterior cricoid plate and then a vertical mattress technique through the membranous wall flap with the knots intended to be outside the lumen. A series of sutures are placed between the laryngeal mucosa and edge of the trachea, taking full thickness bites of the membranous wall flap. The sutures can be placed with the knots on the inside of the lumen. Anterior sutures between the laryngeal cartilage and anterior trachea are placed (7).

Proceeding posterior to anterior, the remaining sutures are tied. The ET tube is advanced past the anastomosis into appropriate position. The thyroid bag is then deflated, the neck is flexed, and the stay sutures are tied first on either side. Then working lateral to medial, the anterior sutures are tied down, finishing in the same fashion with the posterior sutures (2). Thyroid isthmus or strap muscles are buttressed over the anastomosis upon closure.

The integrity of the anastomosis is tested by submerging it under saline and delivering positive pressure via the endotracheal tube. Any defects are approximated with simple interrupted sutures. Approximately 6–7 days later, the patient will undergo surveillance bronchoscopy. Satisfactory examination allows for removal of the guardian chin stitch and diet advancement (2).

Outcomes

Both short and long term results for patients undergoing definitive surgical intervention for ILTS are excellent.

Table 1 Short-term complications (5)

Complications	Number
Anastomotic	36
Granulation	17
Subcutaneous air	7
Stenosis	3
Mucosal flap	3
Cartilage necrosis	2
Bare cartilage	3
Separation	1
Other	84
Wound infection	11
Pneumonia	7
Vocal cord paralysis	2
Swelling requiring steroids	64

Wang *et al.* recently published the largest series in the literature, consisting of 263 patients with ILTS who underwent single stage reconstructive surgery. Just 9% of patients experienced recurrent disease, the majority of which were managed with occasional dilations (5%) and 4% have been recalcitrant requiring repeated dilations. Ninety percent of patients had good results (5).

Post-operative complications were low (*Table 1*). Granulation tissue at the anastomosis and glottic edema are the most common short-term complications (5). Edema typically presents 2 to 5 days postoperatively. Post-operative edema or stridor may be treated with 24–48 h of dexamethasone (2). Diuresis, elevation of the head of the bed, and use of Heliox can be helpful. Granulations usually were successfully debrided with a single bronchoscopy.

Anastomotic complications in this cohort were found to be the most closely associated with previous tracheostomy, stent placement, laser treatment greater than three times, or endobronchial MMC injection (*Table 2*) (5). Further, vocal cord involvement, length of resection greater than 3 cm, and inability to extubate in the OR were risk factors for recurrent disease (5).

A change in voice is experienced by many patients (53%) postoperatively (5). Patients notice a slightly deeper voice or inability to reach high notes if they sing. Their most common problem is a diminished ability to project their voice (67%) (5).

Despite the fact that the etiology of ILTS remains elusive, laryngotracheal resection as a definitive surgical treatment has demonstrated long-term benefits in this patient cohort. This surgical option should be considered early in order to

Table 2 Risk factors for anastomotic complications and recurrence of stenosis (5)

Factor	Complications				Recurrence			
	Univariate		Multivariate		Univariate		Multivariate	
	P	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P	Hazard ratio
Prior tracheostomy (n=59)	0.043	2.6	–	–	0.012	–	–	–
Mitomycin C (MMC) treatment (n=27)	0.013	3.4	–	–	0.026	3.2	–	–
Not extubated (n=16)	0.023	3.7	–	–	0.012	4.4	–	–
Edema + steroids (n=64)	<0.001	4.2	<0.001	6.6	–	–	–	–
Stent (n=5)					0.005	27.5	<0.001	178.0
Laser >3 (n=52)					0.007	3.3	–	–
Length >3 cm (n=18)					0.006	10.2	–	–
Vocal cord abnormality (n=11)					0.001	9.9	0.003	16.8

lessen complications and optimize outcomes.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Uniportal video-assisted thoracoscopic bronchoplastic and carinal sleeve procedures

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Abstract: Despite of the recent advanced with the video-assisted thoracoscopic surgery (VATS), the most common approach for bronchial and carinal resection is still the open surgery. The technical difficulties, the steep learning curve and the concerns about performing an oncologic and safe reconstruction in advanced cases, are the main reasons for the low adoption of VATS for sleeve resections. Most of the authors use 3–4 incisions for thoracoscopic sleeve procedures. However these surgical techniques can be performed by a single incision approach by skilled uniportal VATS surgeons. The improvements of the surgical instruments, high definition cameras and recent 3D systems have greatly contributed to facilitate the adoption of uniportal VATS techniques for sleeve procedures. In this article we describe the technique of thoracoscopic bronchial sleeve, bronchovascular and carinal resections through a single incision approach.

Keywords: Sleeve lobectomy; bronchoplasty; vascular reconstruction; carinal resection; uniportal video-assisted thoracoscopic surgery (VATS); double sleeve

The thoracoscopic approach for major pulmonary resection has numerous advantages compared to open techniques (1-4) without sacrificing the oncologic principles of thoracic surgery. In fact, there is evidence that video-assisted thoracoscopic surgery (VATS) lobectomy may even offer reduced rates of complications and even better survival rates for early stage tumors (5). Future studies will be needed as well to determine if there are advantages for thoracoscopic sleeve resections when comparing with open surgery.

The sleeve procedures offer benefits of parenchymal preservation and oncologic safety even for patients who can tolerate more extensive resections (6). However sleeve resections are technically more demanding than pneumonectomy and are more prone to particular complications (7).

Sleeve procedures are contraindicated when local extension of the tumor requires pneumonectomy as it occurs with involvement of interlobar fissure. The surgeon must identify and avoid reconstructive techniques with risk to develop a severe complication. If the bronchial reconstruction is likely to fail because of the excessive tension or poor anastomotic technique, the result should be carefully evaluated at the end of the procedure, leading to an extensive resection in case of doubt.
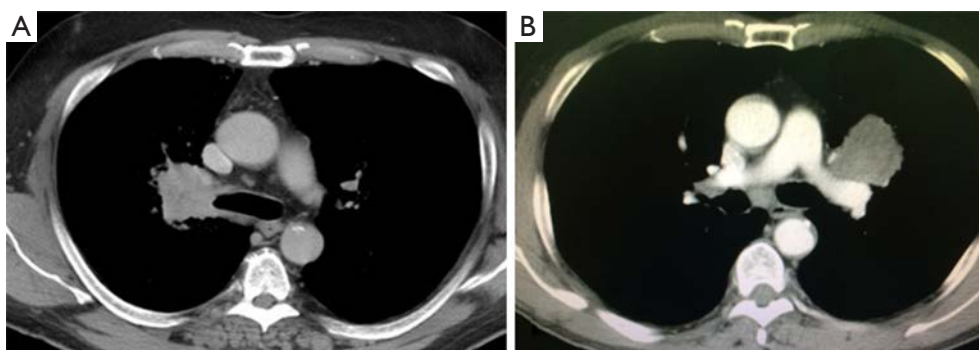
Figure 1 CT scan showing a tumor on the main RUL bronchus (A) and a tumor involving the left main pulmonary (B). CT, computed tomography; RUL, right upper lobe.

Thanks to the recent improvements in thoracoscopy, advanced cases and sleeve resections can be performed without performing thoracotomies (8). During the last years, experience gained through VATS techniques, design improvements of the surgical instruments and improvements of high definition cameras have greatly contributed to advances in VATS (9). Because its approach is less invasive, the uniportal approach for VATS has emerged as a novel technique, applicable to all large spectrum of pulmonary resections including sleeve reconstructions.

In this article we describe the technique of thoracoscopic sleeve procedures through a single incision approach for bronchial, bronchovascular and carinal resection.

Preoperative planning

The indication for a sleeve resection is usually made preoperatively based on computed tomography scan (CT), Positron emission tomography—computed tomography scan (PET-CT) and bronchoscopy (*Figure 1*). Mediastinoscopy or endobronchial ultrasound biopsy (EBUS) should be performed prior to the operation in the case of uptake on PET-CT. The extension of the tumor should be carefully ascertained and histology should be confirmed with biopsy. Preoperative bronchoscopy can identify the need for a sleeve lobectomy when the tumor is at the entrance of a lobar bronchus, or when there are exophytic tumors in a main-stem bronchus or when submucosal signs indicate cancer extension. This diagnostic information is helpful at the time of the surgery when the bronchus is incised and divided. Suitability for surgery should also be assessed, and a pulmonary function test and a perfusion scan performed to predict postoperative lung function are relevant when planning a sleeve.

Typical carcinoid tumors are the ideal cases for sleeve resections. They frequently have a limited base of invasion of the bronchus and the margins do not need to be too large.

During the postoperative management, the patients are usually given antibiotics, humidification or mucolytic and physiotherapy. A bronchoscopy should be performed to check the integrity of the suture and to clear secretions before patient is discharged home.

Surgical thoracoscopic technique

Most of the authors use 3 incisions for the VATS sleeve procedures but the surgery can be performed by using only one (10,11). The patient is positioned in a lateral decubitus position. We consider very important the proper placement of the incision, especially when it is performed by uniportal VATS. Performing the incision at the fourth or fifth intercostal space, more anterior (anterior axillary line), helps to use the needle holder parallel to the hilum, making suturing similar to an open anterior thoracotomy. Using a wound protector is helpful because fatty tissue could interfere with the suture threads (*Figure 2*).

The operating table's position makes the lung exposure easier to perform the anastomosis (the anterior rotation of the table 45° to the surgeon places the lung on an anterior position and makes easier the posterior bronchial suture, especially the membranous portion).

Our preferred method for suturing is to use a continuous absorbable suture (Polydioxanone, PDS 3/0) which makes the thread movement easier, as well as the tying or a novel absorbable barbed suture device, the V-Loc™ wound closure device (Covidien, USA), which avoids knot-tying and keeps strength and security (13). We always test the

Figure 2 Surgical technique for thoracoscopic suturing by uniportal VATS (tying the knots) (12). VATS, video-assisted thoracoscopic surgery.

Available online: http://www.asvide.com/articles/814

Figure 4 Simple bronchoplasty for a right upper lobe endobronchial tumor (15).

Available online: http://www.asvide.com/articles/815

Figure 3 Surgical photo showing instrumentation for bronchial sleeve anastomosis.

anastomosis under saline water and we only place one chest tube at the end of the operation.

When performing bronchial suturing using uniportal VATS, it's very important to maintain the camera on the posterior part of the incision, operating with both hands below the camera. Here we apply the same principle as when performing an anterior thoracotomy in open surgery. That is to have a direct view with the surgeon's eyes above

his/her hands (*Figure 3*). The geometrical explanations of the approach (14) are important factors to facilitate the sleeve reconstructions through a single incision approach. As a result, the anastomosis can be accomplished from a straight perspective in our opinion (*Figure 2*).

We can classify 3 types of bronchoplastic procedures according to the resection type:

(I) Simple bronchoplasty. It is the easiest bronchoplastic procedure. When the tumor is located at the bronchial base, the bronchus is incised at its origin using a long scalpel. For the closure, we use a single PDS 3-0 suture (flushed shape) (*Figure 4*);

(II) Wedge bronchoplasty. In this case the bronchial incision is made deeper in a wedge shape to the main bronchus. This kind of incision may call for a transverse closure, but if the wedge is large and doesn't allow approximation, it may be reconstructed using a lateral closure. The closure stitches are made without tension, and with approximation to the mucosa using a monofilament absorbable interrupted or continuous suture. Recent studies have shown that wedge bronchoplasties, when possible, are a good oncological equivalent to sleeve bronchoplasties, enabling better preservation of the bronchial vascular supply. This is suitable for small tumors with limited invasion of the bronchus, and it allows surgeons with limited experience performing VATS bronchial sleeves to accomplish an oncologic and safe resection (16);

(III) Sleeve bronchoplasty. The bronchial sleeve resections with an end to end anastomosis are the most complex bronchoplastic procedures. The right upper lobe (RUL) bronchoplasty is normally the most frequently performed and less difficult procedure, due to the

Figure 5 Right upper sleeve resection (17).
Available online: http://www.asvide.com/articles/816

Figure 6 Left upper lobe sleeve resection (20).
Available online: http://www.asvide.com/articles/817

alignment of the main and the intermediate bronchi. However, the right bronchus is located at the rear side of the pulmonary artery, and occasionally it is too hidden by the pulmonary artery or the azygos vein which increases the difficulty of the anastomosis (*Figure 1*). The liberation of the pulmonary ligament facilitates lung mobility and reduces tension during and after the anastomosis. For RUL sleeves, the subcarinal lymph node dissection should be performed at the beginning of the procedure. However, the paratracheal lymphadenectomy is preferably done last, after the anastomosis, to prevent the proximal bronchi from retracting under the azygos vein into the paratracheal space, which makes subsequent suturing difficult and requires division of the azygos vein.

The bronchus may be incised initially using a long scalpel, and then the bronchial circumference section may be completed using scissors. Our preferred method is to perform the entire anastomosis using a running

suture in two steps. Usually, the first step is to suture the posterior bronchus wall and then the second step is to suture the anterior wall from behind (inside out) so that both edges are tied at the front level. Another option is a combined technique: interrupted stitches for the cartilage portion of the anastomosis and a continuous suture for the membranous portion. It is best to tie each interrupted stitch before placing the next interrupted stitch to avoid having the free ends of the suture touch each other and get tangled. It is also preferable to tie the knot outwards.

The most complex sleeve procedures are usually those of the left side, due to the presence of the aortic arch and the larger size of the PA. For left-sided bronchial resections, it's best to use a right-sided double-lumen tube in order to make the suturing easier and reduce to the tension on the bronchus.

Right upper lobe (RUL) sleeve lobectomy (*Figure 5*)

Clinical case: 55-year-old male. Squamous cell carcinoma located on the main right bronchus. The patient received 3 cycles of chemotherapy with good response. The incision, 4–5 cm long, was performed on the 4th intercostal space (more convenient for anastomosis on the right side). After division of the vessels and opening the fissure, the right main bronchus, upper lobe bronchus and intermediate bronchus were dissected and sectioned using a long scalpel or scissors (18). The margins were inspected macroscopically and a frozen section was performed before starting the anastomosis. The azygos vein was transected with endostaplers. Sutures were placed on the edge of the main and intermedius bronchus and the bronchial anastomosis was initiated by using a continuous monofilament absorbable 3/0 suture (PDS or V-loc). To compensate the difference of caliber between both bronchi, the interval between the sutures of main bronchus was slightly larger than the intermedius and was adjusted during continuous suture (19).

Left upper lobe (LUL) sleeve resection (*Figure 6*)

The absence of intermediate bronchus, the interference with aortic arch and main PA and the short length of upper lobe bronchus, makes the anastomosis more difficult than on the right side. Care must be taken to avoid injury of the left laryngeal nerve when dissection and anastomosis involves the main bronchus or when complete lymph node dissection of station 5 is performed.
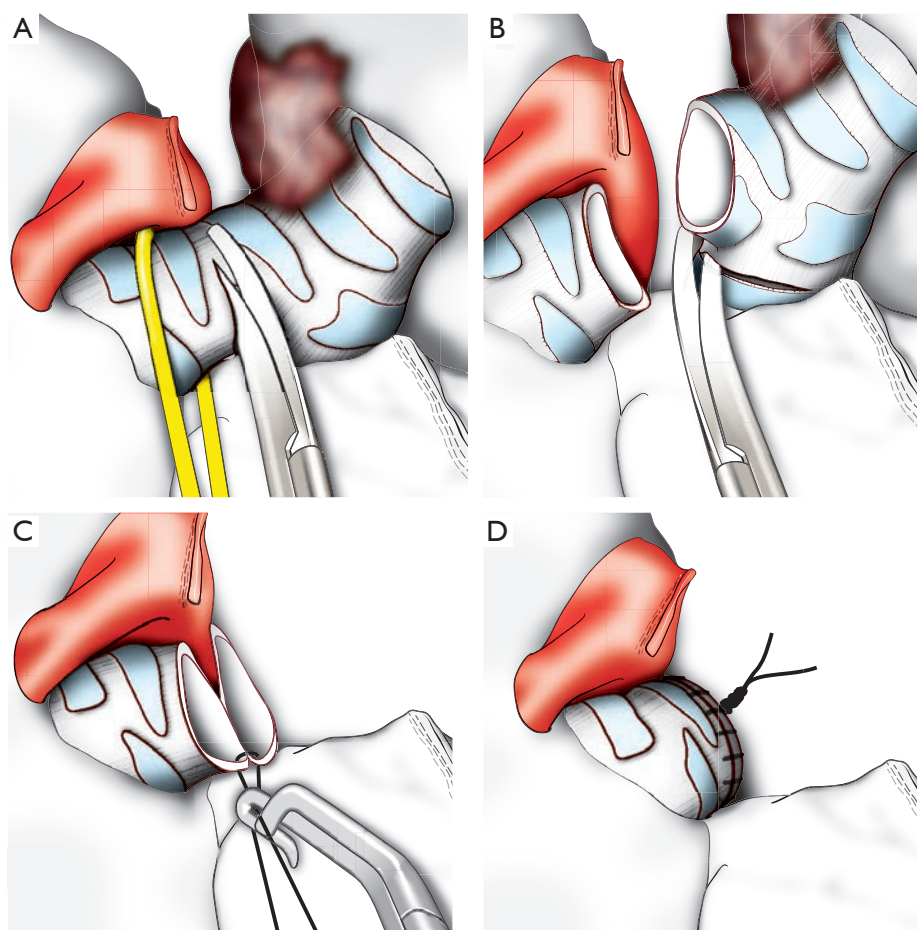
Figure 7 Drawing showing the sequence of lower lobe sleeve resection and anastomosis. (A) Exposure of left upper, lower and main bronchus and transection of LUL bronchus; (B) transection of the main bronchus using scissors; (C) a suture is placed at the angle of anterior portion of both ends of bronchi; (D) final result. LUL, left upper lobe.

Division of the bronchus occurs just proximal and distal to the base of the LUL. Division of the distal end is potentially hazardous because the base of the superior segmental bronchus is next to the LUL's base, and care must be taken not to injure this structure.

The subcarinal lymph node dissection should be performed before the bronchial division. The main bronchus and lower lobe bronchus are initially incised with a long scalpel and then with scissors. The anastomosis is performed as previously described. The running suture technique is performed in two steps: every 180 degree of the 360 degree of the bronchus circumference.

Left lower sleeve anastomosis

The left lower sleeve lobectomy is technically more complex

because of the presence of the pulmonary artery (which should be retracted), the atrium and upper lobe vein. The orientation to perform the anastomosis is also more difficult because the upper lobe bronchus needs to be re-implanted on the main bronchus from an anterior view position, and once we incise the main bronchus is deeply located (10).

The left upper lobe (LUL) bronchus is dissected and exposed. The mainstem and the upper lobe bronchi are cut circumferentially with a knife on a long handle and scissors (*Figure 7*). We commence an end-to-end anastomosis with the first suture in the cartilaginous-membranous junction to help appose the upper lobe bronchi and mainstem bronchi, and then proceeded with a running suture in the posterior wall of airway (the most difficult part of anastomosis). Once the posterior wall of the anastomosis is completed, a running anterior suture is then performed and both sutures

Figure 8 Bronchus intermedius resection (sparing lung) (21).
Available online: http://www.asvide.com/articles/818

are tied with the help of a thoracoscopic knot-pusher.

Bronchial sleeve resection (sparing lung) (*Figure 8*)

Bronchoplastic resections with preservation of parenchyma should be attempted whenever possible when treating distal tracheal or centrally located endobronchial tumors rather than performing a lobectomy, especially for young patients or with poor pulmonary function (22). Generally, the main indications for this surgical technique without lung resection include bronchial low malignant tumors and some benign diseases (23).

VATS lung sparing bronchial sleeve resection is a technically more complex procedure than a standard VATS sleeve lobectomy.

The bronchial anastomosis after a VATS sleeve lobectomy is less difficult to perform as exposure for suturing of the two bronchial ends is easier after removal the lobe (24). The overlying undivided lobar structures limit the exposure for mobilization and sewing during sparing lung sleeve procedures. Compared to the right bronchial sleeve resection, the thoracoscopic reconstruction of the second carina on the left side is usually more complex because the anastomosis of upper and lower lobe bronchus and the left main bronchus is often hidden in the rear of the left pulmonary artery (24).

Clinical case: a 34-year-old young women with an endobronchial carcinoid located on the intermedius bronchus. The main and the RUL bronchus were dissected and exposed. The subcarinal and peribronchial lymph nodes were removed to better expose the anatomy. Once the fissure was divided, the basal artery for lower lobe was taped and retracted. The bronchus intermedius

was incised distally above the origin of the right middle bronchus and proximally just below the origin of the RUL bronchus (*Figure 9*). The anastomosis was commenced by suturing the posterior wall of the bronchus from anterior to posterior direction by using a 3/0 PDS suture. Another continuous suture was done to complete the anterior wall of the anastomosis and both sutures were tied together. The integrity of the anastomosis was tested under saline water. The postoperative recovery of the patient was uneventful and the patient was discharged home on the third postoperative day.

Bronchial sleeve and vascular reconstruction (*Figure 10*)

When the tumor invades the pulmonary artery sometimes it's necessary to resect part of the artery (26,27) or, occasionally a total sleeve (28). The dissection and control of the PA is recommended from the beginning (sometimes intrapericardial control is needed). Before the PA clamping, 5,000 UI intravenous heparin must be administered to prevent thrombosis. We can perform the proximal pulmonary artery clamping with a thoracoscopic clamp. For distal clamping it's better to use bulldog clamps on the artery or clamping the inferior pulmonary vein to interfere as less as possible with the instruments (28). Occasionally, a double vessel loop is enough to clamp the distal artery for partial resections.

When vascular reconstruction is necessary it is advisable that it is done during the last step of the lobectomy (first divide the veins, bronchus and fissure) in order to have a larger surgical field and more control of the section of the pulmonary artery.

The indications for sleeve resection of the pulmonary artery are mostly upper lobe tumors where the tumor or malignant lymph nodes affect the main PA or the upper lobe branches (*Figure 1B*).

A partial resection of the pulmonary artery can be performed especially when the tumor invades the base of one of the lobar branches but without a large involvement (less than 1/3 circumference) into the main PA. After heparinization and clamping of the main artery and distal trunk a tangential incision on the pulmonary artery is performed and a direct closure by means of a running suture with prolene 5/0 or with several interrupted sutures.

In case of vascular sleeve, the bronchial anastomosis should be performed first in order to avoid traction to the vascular suture (*Figure 11A*). The end-to-end vascular
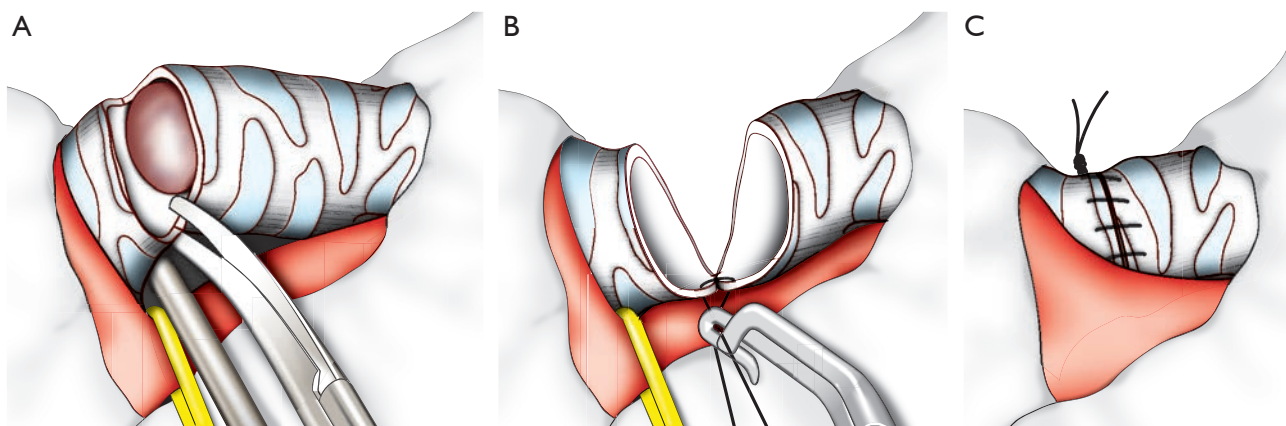
Figure 9 Drawing showing bronchus intermedius bronchial resection and anastomosis (carcinoid tumor). (A) Bronchial distal resection by using scissors (artery is retracted); (B) anterior suture used for apposition of distal and proximal bronchial end; (C) final result.

Video 6. Left upper sleeve resection and vascular reconstruction

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Figure 10 Left upper sleeve resection and vascular reconstruction (25). Available online: http://www.asvide.com/articles/819

anastomosis can be performed with a running monofilament suture (prolene 5/0) in two steps: the first suture line must be the posterior wall of the anastomosis from a back to front direction (*Figure 11B*). Another running suture is used to complete the anastomosis of the anterior wall and it is then tied to the first suture.

Once the vascular suture is completed the distal clamp is removed to release any air thanks to the return flow and tied once the artery is filled. Then a progressive release of the proximal clamp is done.

Carinal resection

Tumors invading the distal trachea or carina represent a challenge due to the complexity of airway reconstruction and management through a thoracoscopic approach (29). The surgical approach for distal trachea or carinal resections

should by the right side (30). A total coordination with the anesthesiologist is paramount during airway resection and a plan in case of emergency should be carefully stablished preoperatively.

To perform this procedure through uniportal VATS, there are two options in order to maintain lung ventilation: the use of an intra-surgical field tracheal tube (31) or through high frequency jet ventilation (32). In the first option a sterile circuit is passed onto the field and prepared to directly ventilate a single lung. For high frequency ventilation jet, the catheter can be introduced through the endotracheal tube and thanks to the small diameter of the catheter for ventilation; it doesn't interfere with the anastomosis of the membranous portion (*Figure 12*). This way we do not need intra-field intubation. Both strategies require a perfect communication with the anesthetics team.

The mode of airway reconstruction depends greatly on the extent of resection. For limited resections of the carina, the right and left mainstem bronchi can be reapproximated to form a "neocarina," which is then attached to the distal trachea. When a right upper lobectomy is necessary with carinal resection, a careful reimplantation of the bronchus intermedius or right lower lobe bronchus to the trachea or left mainstem should be performed to avoid airway necrosis and narrowing. To avoid anastomotic angulation, devascularization, or excesive tension, it is recommended to perform maneuvers for hilar release before the anastomosis. The azygos vein can be transected by using vascular clips (click aV, Grena[R], UK) or endostaplers.

To avoid the aspiration of blood into the left main bronchus, carinal resection should be performed without removing the double-lumen tube. This maneuver allows a
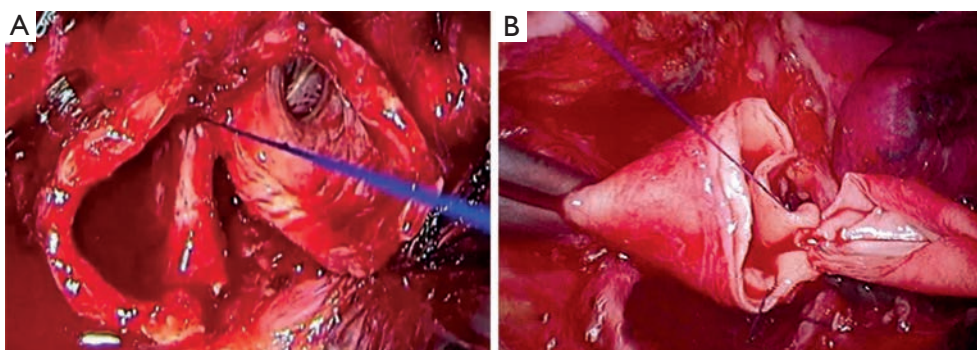
Figure 11 LUL double sleeve lobectomy. (A) Bronchial sleeve; (B) vascular sleeve. LUL, left upper lobe.
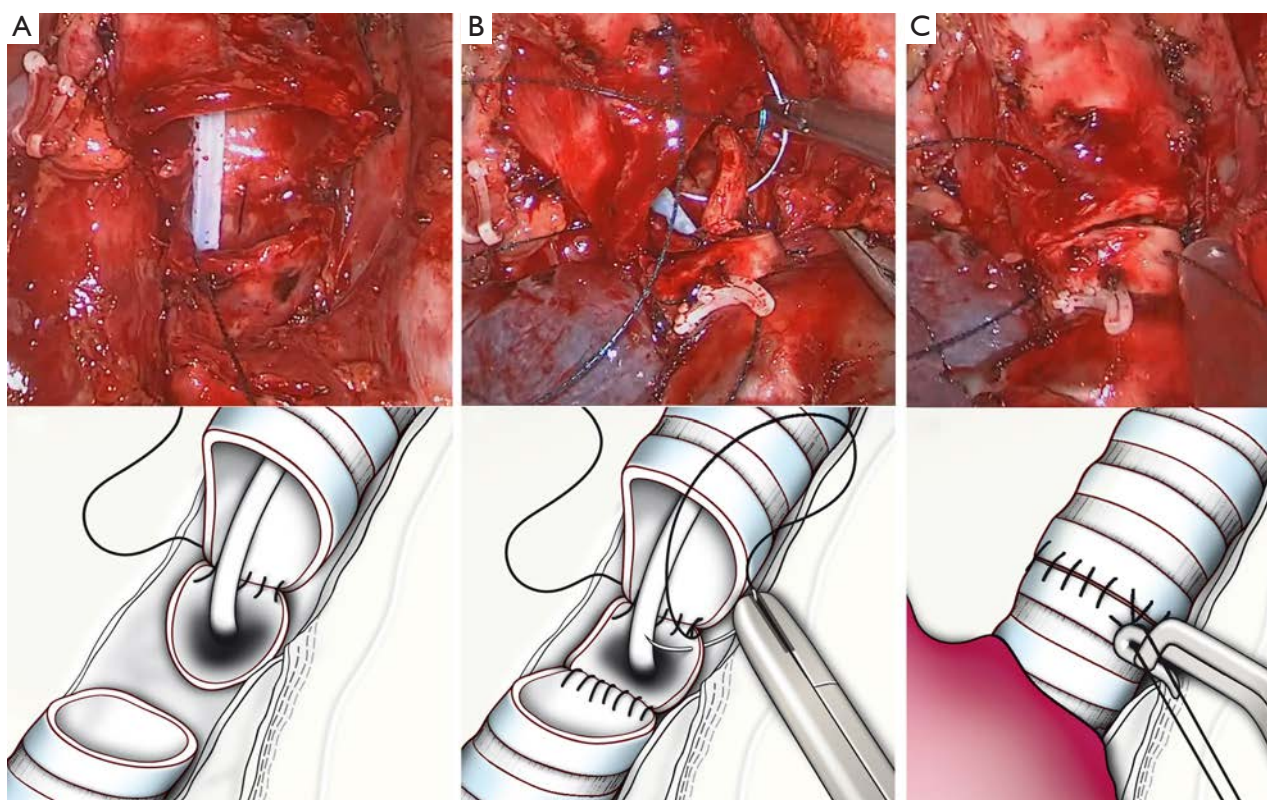
Figure 12 Combined drawings and surgical photos showing carinal reconstruction after right upper sleeve carinal resection. (A) Completed continuous suture of left side wall of the anastomosis between trachea and left main bronchus; (B) after creation of neocarina (left main to intermedius bronchus) the right side wall of the trachea, left main and bronchus intermedius is completed; (C) final result.

safe incision and resection of the distal trachea, right main and left main bronchus. The use of high-frequency jet ventilation of the left lung is useful to maintain oxygenation and facilitates the anastomosis of the left side wall of the main stem bronchus and distal trachea, avoiding the insertion of a tracheal tube through the incision (33).

The suture should be commenced first suturing the left side wall of the trachea and left main bronchus (*Figure 12A*). Then sutured membranous trachea and left main bronchus. Then neo-carina of left main bronchus and right main (in case of pure carinal resection) or intermediate bronchus (in case or RUL and carinal) (*Figure 12B*). Finally the right side wall of the trachea, left main bronchus and right bronchus should be anastomosed (33) (*Figure 12C*). It is
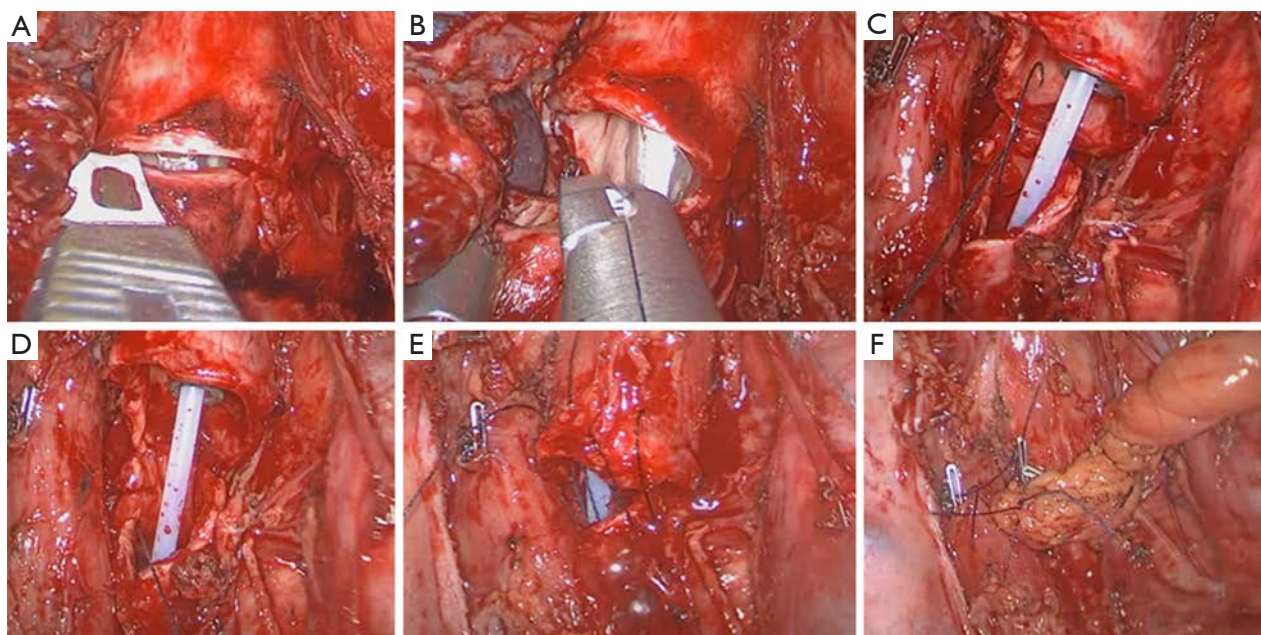
Figure 13 Surgical images of right carinal pneumonectomy. (A) The distal trachea is incised; (B) the circunferencial resection is completed by using scissors. (C) the running suture was started on the left wall of the trachea and left main bronchus; (D) the membranous portion was anastomosed after the left wall was completed; (E) the right side of the trachea and left main is performed; (F) a pericardial flap covered the anatomosis.

recommended to cover the suture with a pericardial flap.

Another option is the resection of the carina, followed by a total end-to-end anastomosis between the left main bronchus and the trachea with an anastomosis of the right main bronchus to the lateral, cartilaginous wall of the trachea (at least 2 cm above the first anastomosis).

When carinal reconstruction can not ensure a tension-free anastomosis, the safest option is to perform a carinal pneumonectomy (if patient tolerate the procedure) by doing an end-to-end anastomosis of the trachea to the remaining mainstem bronchus (*Figure 13*). The suture should be commenced first suturing the left side wall of the trachea to the left side wall of the left main bronchus, then membranous portion and finally right side of trachea and left main bronchus.

We have analyzed our experience with double sleeve and carinal resections in conjunction with the Tyumen Regional Oncological Center (Russian Federation). To date we have performed 10 cases (8 male, 2 female) with a mean age of 61±4.6 years (range, 48–68 years): 7 uniportal VATS double-sleeve resections (6 left upper lobectomy, 1 RUL) and 3 uniportal carinal resections (2 RUL and 1 sleeve pneumonectomy). Three cases of uniportal double-

sleeve lobectomy and one case of uniportal carinal resection received neoadjuvant chemotherapy (gemcitabine + cisplatinum). The mean operative time was 260±20 min (range, 240–330 min) and the mean intraoperative blood loss of 235.5±55.6 mL (range, 50–460 mL). The mean number of lymph nodes resected was 13.12±5.13 (range, 12–20). The mean postoperative hospital stay was 10±1 days (range, 7–20 days). Two cases of double-sleeve lobectomy developed postoperative pneumonia but were succesfully treated with intravenous antibiotics. There was no postoperative 60-day mortality in this serie of patients.

Discussion and literature review

Minimally invasive surgery for cancer has proven to offer many benefits over traditional open surgery, including less pain and faster recovery without compromising oncologic results (1-5). VATS has evolved from the conventional three-port technique to the uniportal approach during the last decade (34).

Thanks to the increasing experience with thoracoscopic suturing, tying techniques and development of new instruments, the bronchoplastic procedures can be performed

thoracoscopically by expert surgeons (33,35,36). There are many publications showing that an open sleeve lobectomy results in a better survival rate than pneumonectomy, a reduced loss in lung function, and an improved operative mortality (37,38). The first description of a VATS sleeve procedure was published 15 years ago by conventional VATS (39). The concerns about performing an oncologic resection and a safe anastomosis when bronchoplasty is needed are the main reasons for the slow adoption of the technique. This limits the number of surgeons that are able to master the sleeve technique by VATS. Some authors consider a minimum number of 25 cases for overcoming the learning curve and safely perform locally advanced cases by VATS (40).

Like all other procedures, VATS sleeve lobectomy has its natural learning curve. According to our own experience, at least more than 200 VATS lobectomies and at least 20 cases of open sleeve procedures should be done in order to lay the anatomical and operative technique foundation, before you can perform a thoracoscopic sleeve resection (41).

The principles of the VATS bronchoplasty are the same as for open surgery (37). The anastomosis must be performed free of tension for mucosa to mucosa approximation. We recommend using monofilament absorbable sutures for smooth placement and sliding of knots (non-absorbable sutures can irritate the airway and cause significant postoperative cough). A critical technical issue is the management of the sutures to avoid the tangling of the untied ends. The management of the instruments and sutures is more crucial in VATS than in an open thoracotomy. The tension of the suture can be carefully adjusted with a sliding knot-pushing instrument.

Some authors recommend interrupted sutures to allow better size matching, less anastomotic site ischemia and prevent the loosening and entanglement of the sutures (42).

Other authors improved the suturing technique by using both continuous and interrupted suturing, for the membranous and cartilaginous portions of the bronchus respectively (43). In our particular experience a continuous suture performed in two steps for the posterior and the anterior bronchial wall results in less suture tangling and is quicker (33,35). A novel absorbable barbed suture device, the V-Loc™ wound closure device can be used to avoid knot-tying (13).

We routinely do not buttress the suture unless the case was after radiation or presented with signs of infection (44). In these cases we can use an intercostal muscle flap, pedicle pericardial or mediastinal fat pad.

There are few articles published in the literature describing bronchial, vascular or combined bronchovascular sleeve by VATS, and most of these resections are reported by using conventional thoracoscopic techniques (45,46). As our experience has grown with the uniportal VATS approach we have increased the rate of these reconstruction techniques and decreased the incidence of pneumonectomy (27-29,33,34). In a recent publication, we assessed the feasibility of uniportal VATS approach in the treatment of advanced NSCLC and compared the perioperative outcomes with early-stage tumors with good postoperative results (47).

There are several case reports of NSCLC sleeve procedures of the RUL by using 4 ports (48), 3 ports (49,50) or 2 ports (51). Mahtabifard *et al.* reported a series of 13 sleeve resections. Median operative time was 167 min (range, 90–300 min) and chest tube duration was 3 days (range, 2–6 days). Morbidity was 31% (42).

Yu *et al.*, reported case series of 9 bronchial thoracoscopic sleeve lobectomies performed through four ports. The authors modified the technique from interrupted sutures in the first cases to a continuous suture combined with discontinuous anastomosis in the late surgeries. The mean surgical time was 203±20 min. Two 28F chest tubes were placed at the end of the operation. The total duration of hospitalization lasted, on average, 20.8 ± 2 days. No recurrences or severe complications were reported (52).

Agastian *et al.* reported 21 VATS bronchoplastic procedures (9.1% of all VATS in his serie) including wedge (9), sleeve bronchoplasty (8) and other extended bronchoplasties (4). The authors used an interrupted suture technique for anastomosis. Mean surgical time was 287 min (range, 135–540 min), mean hospital stay was 5.2 days. Most of the cases were NSCLC (24). All brochial margins were negative for malignancy. Only one patient developed broncho pleural fistula and in a follow up of 26 months there was no tumor recurrence (36).

Xu *et al.* reported 20 sleeve lobectomies (including a RUL sleeve resection combined with half-carinal reconstruction and right medial lung sleeve resection combined with lower right dorsal segment). The average time of surgery was 239±51 min (range, 142–330 min), and the average time of airway reconstruction was 44±17 min (range, 22–75 min). The median postoperative hospital stay was 10 days (range, 8–12 days). None of the patients developed anastomotic leak and perioperative mortality was not observed. The bronchial suture was initially performed with a modified interrupted suture and subsequently with a continuous suture during which the membranous posterior

and the cartilage wall were anastomosed with single 3/0 polypropylene suture (53).

The serie of Li *et al.* included 15 VATS sleeve lobectomies with bronchoplasty for NSCLC (RUL 10, right middle and lower lobes 1, left lower lobe 2 and LUL 2) by using 3 ports. The authors describe the technique for anastomosis by using a simple continuous and simple interrupted suturing of the membranous and cartilaginous portions of the bronchus. All procedures were uneventful, (only 1 minor complication) with a median operative time of 165 min (median bronchial anastomosis time of 44 min). The median duration of chest tube drainage was 5.4 days, and the median length of hospital stay was 7 days. All patients were followed postoperatively for a range of 1–16 months without tumor recurrence (43).

When experience is acquired with VATS, more advanced procedures such as double sleeve, tracheal or carinal resection can be performed by using even only a single incision (33). A perfect planning of the operation and coordination with the anesthesiologist are mandatory when dealing with these cases. The use of uniportal VATS for reconstructive surgery represents a challenge for the thoracic surgeon because of the technical difficulties for anatomic reconstruction, vascular and airway management.

There are few publications of VATS double sleeve procedures reported in the literature (54,55). Our group published several case reports of bronchoplastic procedures including vascular reconstruction (27) and double bronchial and vascular sleeve procedures (28,33). Huang *et al.* showed a retrospective multi-center study with thirteen thoracoscopic double sleeve resections for NSCLC patients. There were no conversions to thoracotomy. The median operative time was 263 min and the median postoperative hospital stay was 10 days (55).

The thoracoscopic technique for other complex procedures such as tracheal or carinal sleeve resections has recently been described (33). The classic approach for carinal reconstruction is the right thoracotomy or median sternotomy (29) but these complex procedures can be also performed by uniportal VATS through the right side. After carinal or tracheal resection, ventilation can be maintained by using a high ventilation jet (32) or by using an intraoperative single lumen tube (through the uniportal incision or adding an additional 1 cm skin incision). For resection of the distal trachea or carina, the left and the right main bronchus can be re-approached to create a new carina and then re-anastomosed to the trachea (33).

Conclusions

Thanks to the acquired experience with minimimally invasive techniques such the uniportal VATS, the broncoplastic procedures and even the most complex reconstructions including VATS broncho-vacular sleeve and carinal resections can be performed safely. These procedures must be performed as an alternative to pneumonectomy ensuring a safe anastomosis and complete tumor resection. Further studies will be necessary to evaluate the long term results of a large serie of these complex resections operated by uniportal VATS.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Video-assisted thoracoscopic surgery resection and reconstruction of thoracic trachea in the management of a tracheal neoplasm

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Abstract: Intratracheal tumor is a rare tumor, accounting for only 2% of upper respiratory tract neoplasms. Its symptoms are similar to those of head and neck cancers, including coughing up blood, sore throat, and airway obstruction. The diagnosis of this disease is often based on the findings of fibrobronchoscopy or computed tomography (CT). Surgery remains the treatment of choice for tracheal tumor. In patients with benign neoplasms or if the tumors have limited involvement, fibrobronchoscopic resection of the tumor can be performed. For malignant tumors, however, radical resection is required. In the past, open incision is used during the surgery for tumors located in thoracic trachea. Along with advances in video-assisted thoracoscopic surgery (VATS) minimally invasive techniques and devices, VATS resection and reconstruction of the trachea can achieve the radical resection of the tumor and meanwhile dramatically reduce the injury to the patients. In this article we describe the application of VATS resection and reconstruction of trachea in the management of a tracheal neoplasm.

Keywords: Tracheal tumor; surgery; video-assisted thoracoscopic surgery (VATS); resection; video-assisted; thoracoscopy

Introduction

Surgery remains the treatment of choice for tracheal tumor. The purpose of surgery is to completely resect the tumor and the adjacent tracheal tissues that have been invaded by the tumor, followed by the anastomosis of the distal and proximal ends of the trachea to finalize the tracheal reconstruction. In the past, open incision is used during the surgery for tracheal tumors: for tumors located in the cervical trachea, the incision is made in the neck; for tumors located in the thoracic trachea, however, the incision is often made in the left or right chest. Along with advances in video-assisted thoracoscopic surgery (VATS) minimally invasive techniques and devices, VATS lobectomy or even total pneumonectomy has become possible. However, few literatures have reported the VATS tracheal resection and reconstruction for tracheal masses. To achieve radical resection of tracheal tumor and meanwhile reduce the injury to patients, we describe the application of intubated VATS tracheal resection and reconstruction in the management of a tracheal neoplasm, with particular focus on the anesthesia and operation skills during the surgery.

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Case presentation

Patient

A 60-year-old non-smoking male patient developed progressively worsening cough, hemoptysis, and shortness of breath in the past 1 month. Chest computed tomography (CT) showed a space-occupying lesion inside the upper trachea, along with the stricture of the corresponding tracheal lumen. Low-grade malignant tumor or benign lesion was considered. The mass was sized 2.5 cm × 2 cm × 2 cm and located at the level of the second thoracic vertebra (*Figure 1*). Multiple bullae were seen at the apex of the right upper lobe, whereas fibrous lesions were visible at the apexes of both upper lungs and the basal segment of left lower lobe. Whole-body bone scan showed no abnormality. Plain CT scans of head and abdominal organs did not find any suspicious lesion. Pulmonary function tests showed decreased FEF 25–75%, MEF 50%, and MEF 25%, whereas the pulmonary ventilation function was basically normal.

Anesthesia

After the induction of general anesthesia, the patient was under endotracheal intubation. Sufentanil (10 μg) and propofol (80 mg) were used for anesthetic induction. Muscle relaxant vecuronium (0.1 mg/kg) was applied. Ventilation with tracheal intubation was applied when spontaneous breathing stopped. Tracheal intubation was completed under the guidance of fibrobronchoscope. Touching of the intratracheal mass by the tracheal tube should be avoided. The tracheal tube was connected with the anesthesia ventilator for mechanical ventilation. The oxygen concentration was adjusted according to blood oxygen saturation to maintain the blood oxygen saturation above 95%. During the surgery, anesthesia was maintained using remifentanil (0.03–0.05 μg/kg per min) and propofol (0.2 mg/kg per min). In addition, the anesthesiologist also prepared devices for intrathoracic tracheal intubation, which was used to maintain oxygen supply during tracheal reconstruction. The depth of anesthesia was measured using the EEG bispectral index during the surgery.

Surgical process

The patient was placed in a left lateral decubitus position. A 1-cm observation port was made in the 6th intercostal space at right anterior axillary line for the placement of 30°

thoracoscope. In addition, two incisions (2.5 and 0.5 cm in length, respectively) were made in the 3rd intercostal space at anterior axillary line and in the 7th intercostal space at posterior axillary line as the operation ports. During the surgery, we found that the collapse of the operated lung was good; then, the lung was lifted forwards to achieve good surgical field. Mediastinal pleura was cut open using HIFU, and the trachea from the level of suprasternal notch to that of carina was dissociated (*Figures 2,3*). After the trachea was suspended using rubber tubes and sutures (*Figure 4*), the distal end of the trachea that was about 1.0 cm away from the tumor edge was dissected (*Figure 5*); meanwhile, the tracheal tube with a balloon was inserted via the thoracic cavity to ensure the patency of airway (*Figure 6*). Then, the trachea was transected at the proximal end of the tumor to completely resect the tracheal mass (*Figures 7,8*). Intra-operative frozen section analysis showed that the surgical margin was negative. The mass was pathologically confirmed to be low-grade malignant epithelial tumor. Reconstruction of the trachea was completed by continuous end-to-end anastomosis of the stumps using 2–0 Prolene sutures (*Figure 9*). After the reconstruction of the posterior wall of the trachea was completed, the tracheal tube was withdrawn via the thoracic cavity and then inserted via mouth (*Figure 10*), so that the reconstruction of the lateral and anterior walls of the trachea could be completed (*Figures 11,12*). The anastomotic leak test was performed using sterile saline (*Figure 13*). After it was confirmed that there was no anastomotic leak or intrathoracic active bleeding, we closed the chest incisions, while two chest tubes (up and down) were remained in the thoracic cavity for drainage. The intraoperative SpO_2 was maintained between 97% and 100%. Blood gas analysis showed that the patient had no non-respiratory acidosis. The patient's vital signs remained stable throughout the operation.

Postoperative conditions

Postoperative chest X-ray showed that the operated lung was well reexpanded and there was no sign of pneumothorax. The patient occasionally had cough and sputum production but did not have symptoms such as shortness of breath, chest pain, or dyspnea. He complained of pain at the site of chest tube placement. Non-steroidal anti-inflammatory drugs and ambroxol were administered to alleviate the symptom. The patient did not experience any surgery-related complication. The chest tubes were withdrawn on the third postoperative day, and the
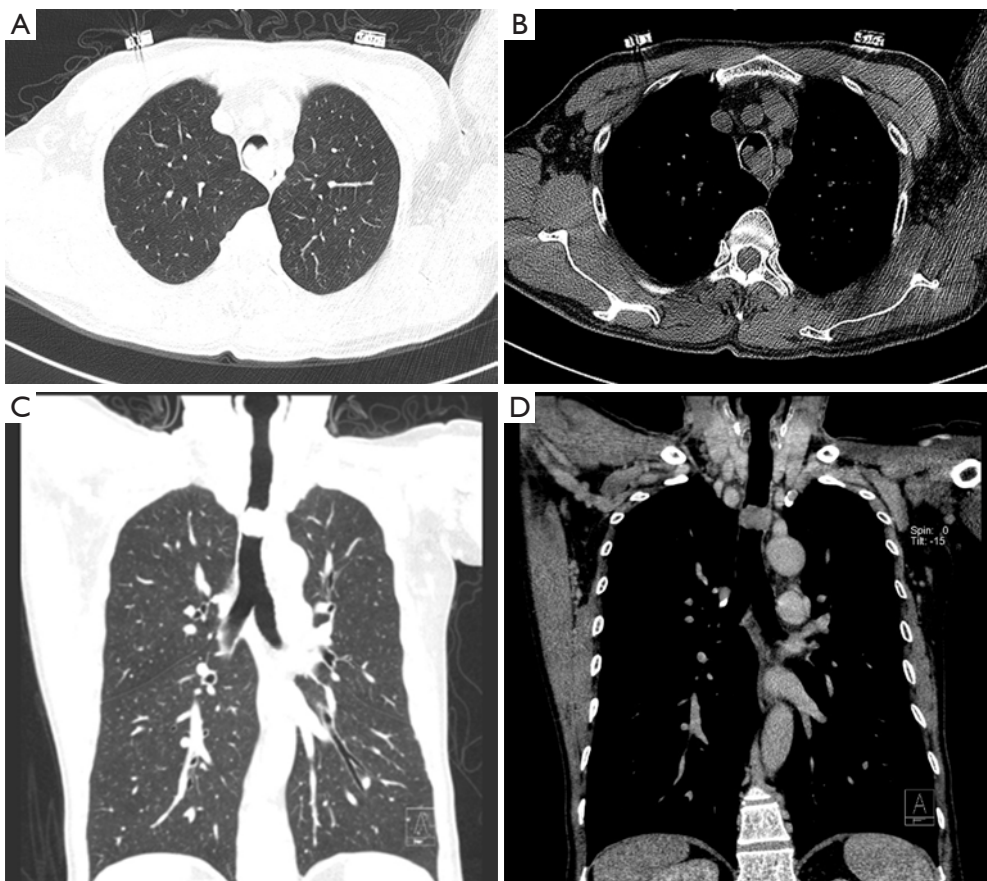
Figure 1 The preoperative computed tomography (CT) showed a mass inside the middle portion of the thoracic trachea; the tracheal lumen where the mass was located became obviously narrow, and the mass blocked most of the tracheal lumen.
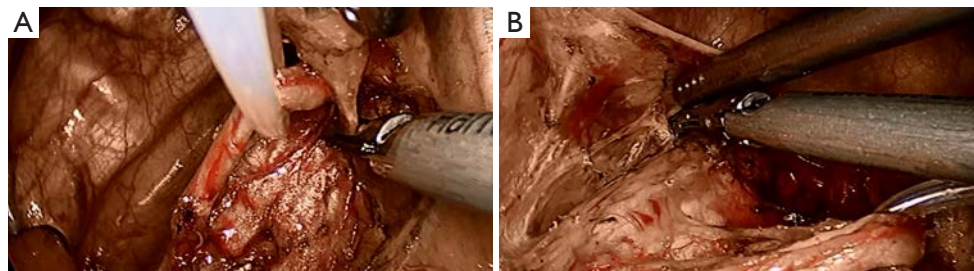

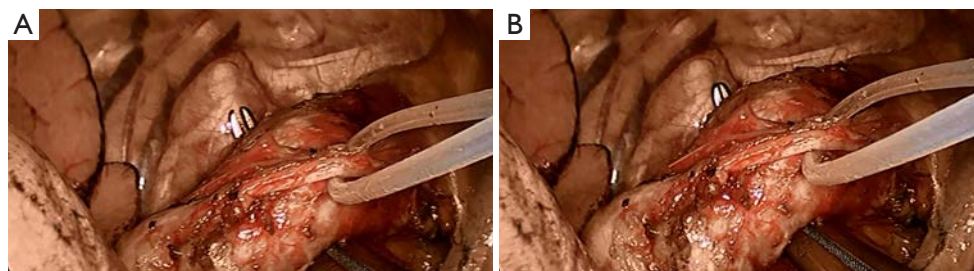**Figure 2** Open the mediastinal pleura to dissociate thoracic trachea.

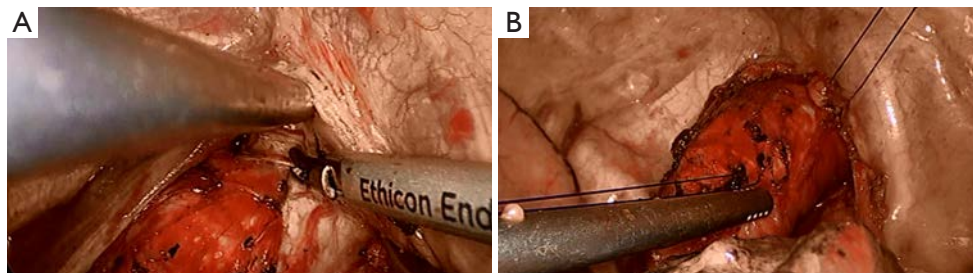**Figure 3** Disassociate the tissues behind the thoracic trachea.

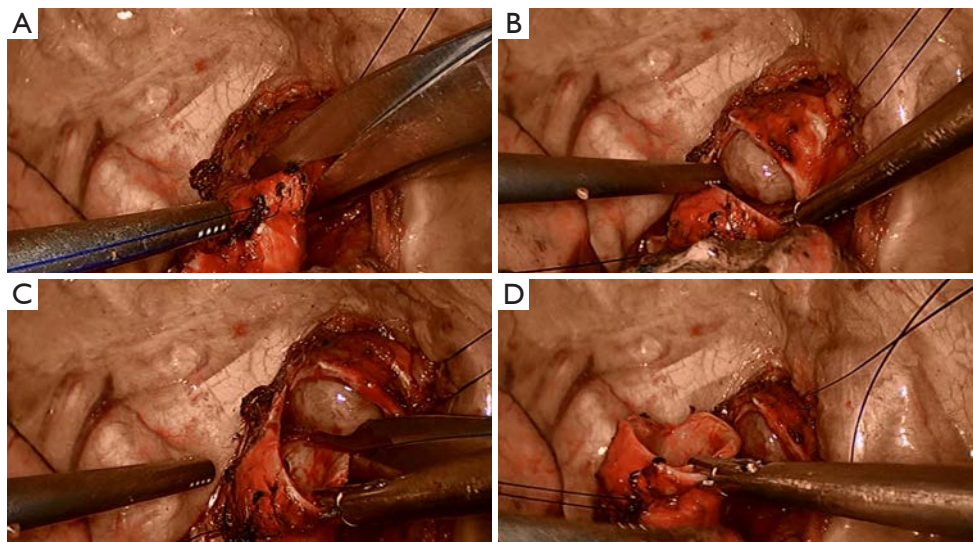**Figure 4** Thoroughly dissociate the trachea and then suspend it using a suture.

Figure 5 Cut the trachea at distal end of the tumor using tissue scissors. It was found that the roundish tumor had smooth surface and was latticed with tiny blood vessels; it was not obviously lobulated, showing a translucent status.
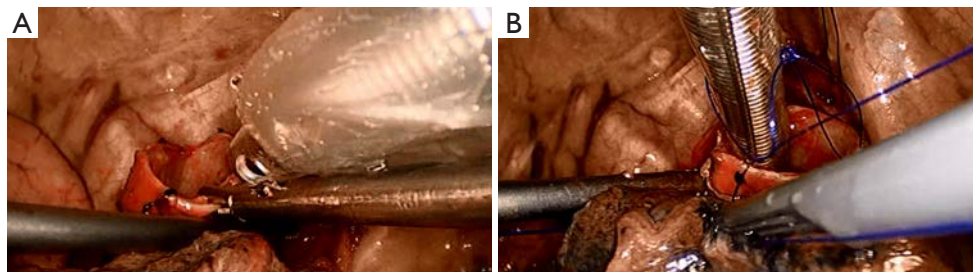
Figure 6 The tracheal tube was placed at the distal stump via the thoracic cavity and then fixed with sutures.
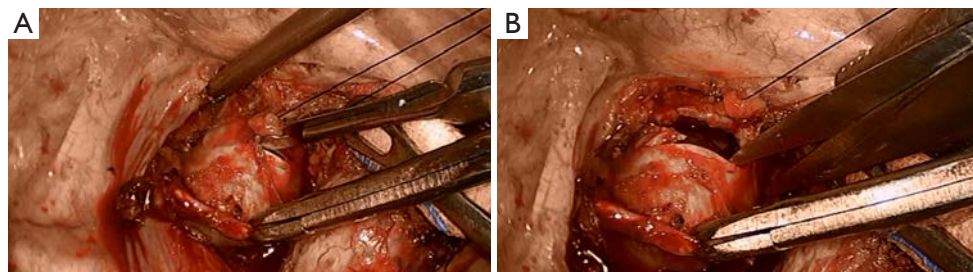
Figure 7 The trachea was cut open at the proximal end of the tumor using a scalpel, and the proximal stump was pruned using tissue scissors.

Figure 8 The posterior wall of the trachea was divided using HIFU to achieve the en bloc resection of the tumor and the involved part of the trachea.

patient was discharged on the seventh postoperative day. The patient was advised to avoid any strenuous activity. Meanwhile, he was advised to keep his head in a lower neutral position, so as to prevent hyperextension of his neck. During the 3-month follow-up, the patient had good general conditions and did not complain of any respiratory symptom.

Postoperative diagnosis

The final pathological diagnosis was: low-grade adenocarcinoma in the trachea (*Figure 14*).
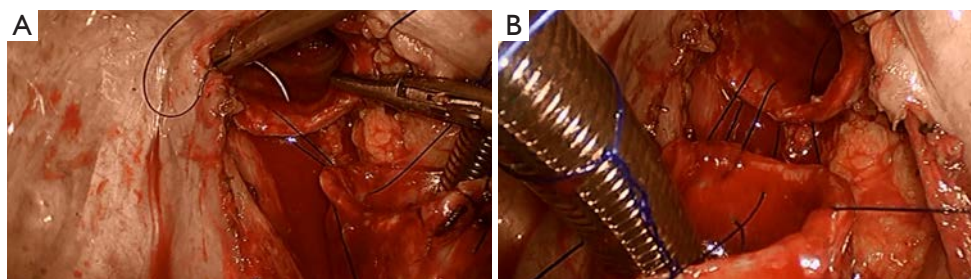
Figure 9 The posterior wall of the trachea was continuously closed using the 2–0 Prolene sutures.

Figure 10 The tracheal tube was withdrawn via the thoracic cavity and then inserted via mouth.
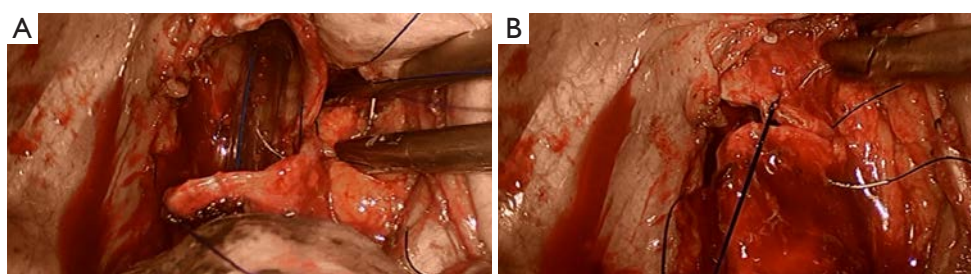
Figure 11 The anterior wall of the trachea was continuously closed using the 2–0 Prolene sutures.
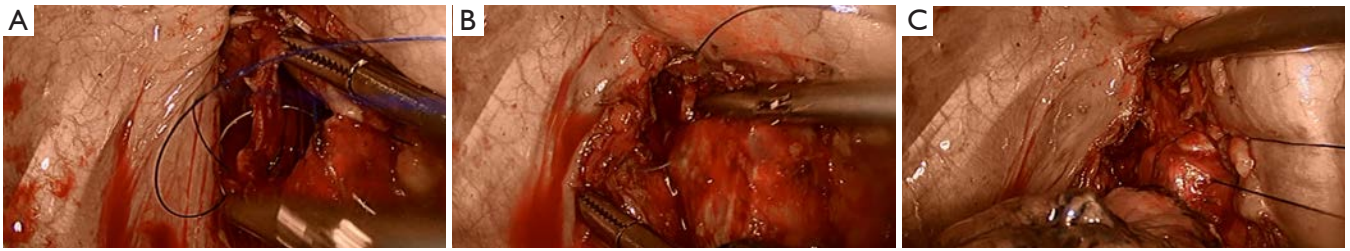
Figure 12 The lateral wall of the trachea was continuously closed using the 2–0 Prolene sutures.
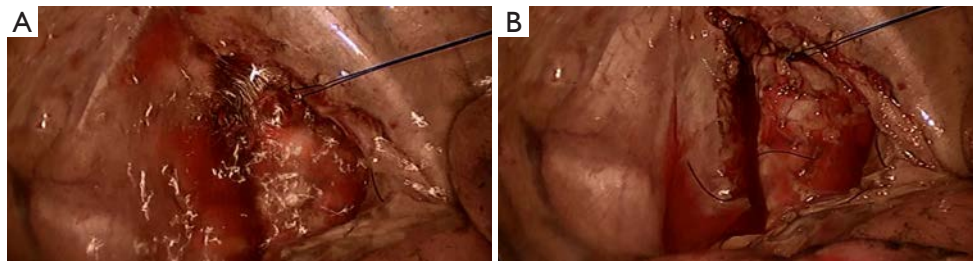
Figure 13 Anastomotic leak testing; knots were tied and fixed after the anastomosis was confirmed to be leak-free.
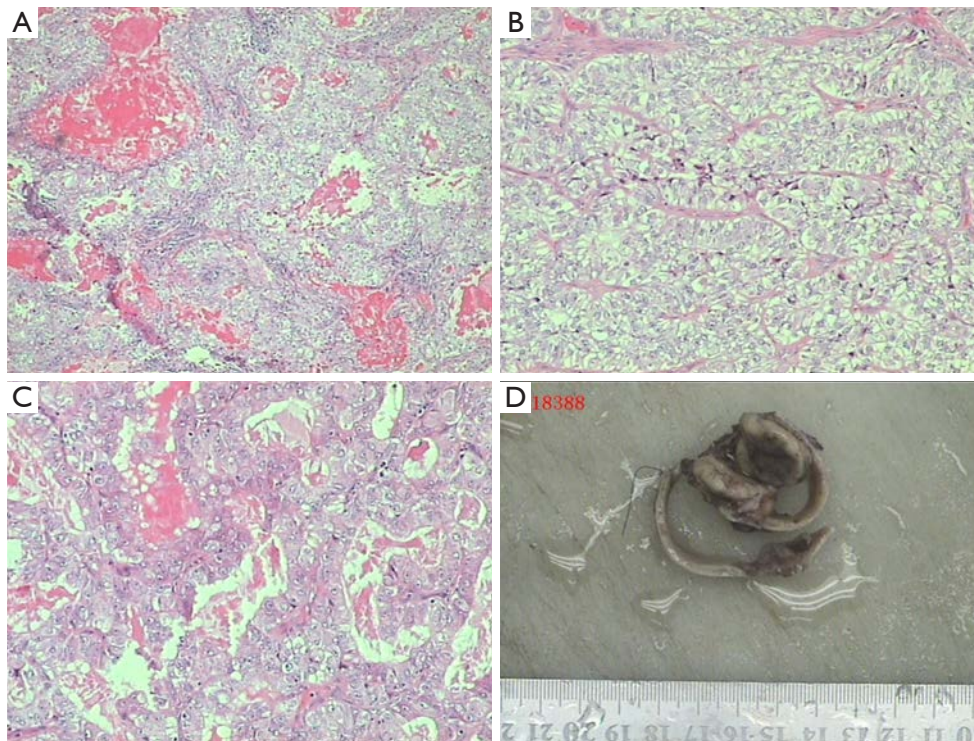
Figure 14 Pathology: the tumor tissue was adhered to the tracheal wall and had relatively clear boundary with the wall. The tumor cells showed acinar-like architecture, with clear cytoplasm. The cytologic atypia was not obvious, and no mitotic figure was observed. Within the acinar lumen there were a large number of mucus-like secretions. The lesion was confirmed to be low-grade malignant adenocarcinoma that might have been arisen from tracheal glands (magnification, ×100).

Figure 15 Video-assisted thoracoscopic surgery (VATS) resection and reconstruction of thoracic trachea (1).

Available online: http://www.asvide.com/articles/912

Immunohistochemistry: CK (+), EMA (+), CEA (–), S100 (–), Syn (–), CgA (–), Cd56 (–), CK7 (+), Napsin A (–), TTF1 (–), Calponin (–), P63 (–), CK5/6 (–), P40 (–), Cd10 (–), Vim (+), CK20 (–), CDX2 (–), PAX-8 (–), PSA (–), HMB45 (–), Ki67 (about 5%).

Special staining: mucicarmine staining (+), periodic acid-Schiff (PAS) digest stain (+), AB (+), and PAS (+).

Lymph nodes: station 1 (0/2), station 2 (0/5), and station 2/4 (0/1).

The detail of the surgical process was demonstrated in the video (*Figure 15*).

Discussion

Tracheal tumor is a relatively uncommon tumor of upper respiratory tract (2). Typically it is less malignant and is often localized within tracheal lumen. The common symptoms of tracheal tumors include cough, coughing up blood, shortness of breath, and wheezing. However, some patients can also be asymptomatic. When the tumor becomes larger, the patient may suffer from difficulty breathing or even asphyxia (2-4). Therefore, early diagnosis and early treatment are particularly important for tracheal tumors. A variety of treatment methods including fibrobronchoscopic tumor resection, radiotherapy, and conventional surgical resection have been development for tracheal tumors (5). However, the preferred radical treatment remains the complete resection of the tumor followed by tracheal reconstruction.

However, this surgery is somehow difficult due to various reasons. First, the thoracic trachea is located above the thoracic outlet and approaching the apex of cervical pleura, which are surrounded by many vital structures such as the superior vena cava. Therefore, the operation range is relatively small, and the surgical field is somehow limited. Second, part of the trachea needs to be resected before reconstruction. Thus, to ensure oxygen supply during the surgery, the anesthesiologist needs to withdraw the orally inserted tracheal tube during the resection of tracheal tumor; meanwhile, the operator must insert another tracheal tube into the distal end of trachea via the thoracic cavity to ensure the patency of airway. During tracheal reconstruction, the anesthetist needs to insert a new tracheal tube by mouth, whereas the operator must remove the transthoracically inserted tracheal tube (6). Furthermore, the anesthesiologist needs to continue to place the transorally-inserted tracheal tube to the distal end of the trachea to ensure the tube pass through the anastomosis. Due to the complexity of the procedure, the operator must have rich and solid experiences and skills in endoscopic suturing, along with close cooperation with the anesthesiologist.

In summary, VATS resection and reconstruction of trachea in the management of tracheal mass have certain advantages: (I) it reduces the surgery-related injuries; and (II) the zoom-in function of the thoracoscope enables finer suturing. However, it's the surgical field is near the apex of pleural cavity, the visual field and surgical range are somehow limited. It remains a highly challenging procedure for most medical teams.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Video-assisted transthoracic surgery resection of a tracheal mass and reconstruction of trachea under non-intubated anesthesia with spontaneous breathing

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Abstract: Radical surgery for tracheal tumors is typically completed under basal anesthesia. Thus, endotracheal intubation and mechanical ventilation are required. However, these procedures may influence the surgical operation and meanwhile prolong the surgical duration and postoperative recovery. In this article we describe the application of video-assisted transthoracic surgery (VATS) resection of a tracheal mass and reconstruction of trachea a non-intubated patient with spontaneous breathing.

Keywords: Tracheal mass; video-assisted transthoracic surgery (VATS); non-intubated; surgery; spontaneous respiration

Introduction

The application of video-assisted transthoracic surgery (VATS) for tracheal diseases has been reported in literature, showing satisfactory effectiveness (1,2). However, these surgical procedures typically require endotracheal intubation, chest intubation, and mechanical ventilation. Some recent articles have reported the use of segmentectomy or lobectomy in non-intubated patients with spontaneous breathing (3-5). They found that these lung surgeries were feasible and safe. In our center we have completed segmentectomy or lobectomy in more than 250 non-intubated patients with spontaneous breathing. Thus, we have accumulated rich experiences in dealing with the relevant complications and unexpected situations. In addition, repeated intubation is needed for patients undergoing surgeries for tracheal neoplasms. In order to minimize the injuries caused by endotracheal intubation and mechanical ventilation and speed up the postoperative recovery, we performed the VATS resection of a tracheal mass and reconstruction of trachea in a non-intubated patient with spontaneous breathing.

Case presentation

Subjects

A 44-year-old non-smoking female patient developed progressively worsening shortness of breath with decreased body weight in the past 2 months. She had progressive dyspnea and intermittent orthopnea. Chest computed tomography (CT) showed a tracheal mass located at the T2 and T3 vertebrae, about 3 cm away from the carina. The mass could be clearly seen under contrast-enhanced CT, with a size of 2.0 cm × 1.6 cm × 1.2 cm (*Figure 1*). Bronchofiberscopy showed that there was a lobulated mass
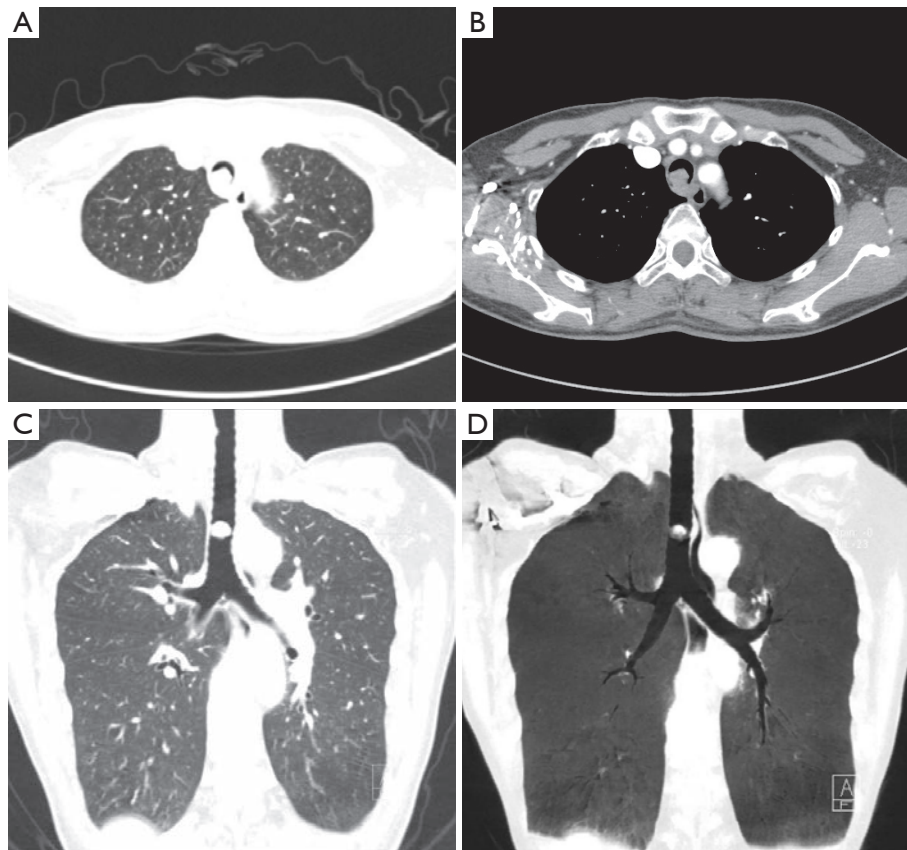
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Figure 1 Preoperative computed tomography (CT) indicated a mass sized 1.2 cm × 1.3 cm on the right posterior wall of the mid-lower trachea (6 cm away from carina). The mass protruded into the tracheal lumen, resulting in airway blockage and stenosis.

Figure 2 Preoperative fibrobronchoscopy showed a mass sized 1.2 cm × 1.3 cm on the right posterior wall of the trachea (about 8 cm away from glottis). The mass had a gray-yellow surface, with congestive basal part. It protruded into the tracheal lumen, resulting in airway blockage and stenosis.

inside the trachea, and the tumor almost complete blocked the trachea (*Figure 2*). Since the shortness of breath and dyspnea were gradually worsening, bronchofiberscopic resection of tracheal tumor was performed to alleviate the respiratory symptoms (*Figure 3*). The postoperative pathology confirmed that the lesion was a mucoepidermoid carcinoma. A second postoperative chest CT indicated that the residual tumor inside the trachea had invaded the entire posterior wall of trachea (*Figure 4*). In order to achieve satisfactory effectiveness of radical treatment, we further discussed the disease condition and treatment protocol with the patient and her family and with other colleagues in our department and then decided to carry out VATS resection of tracheal mass and reconstruction of trachea under non-intubated anesthesia with spontaneous breathing.
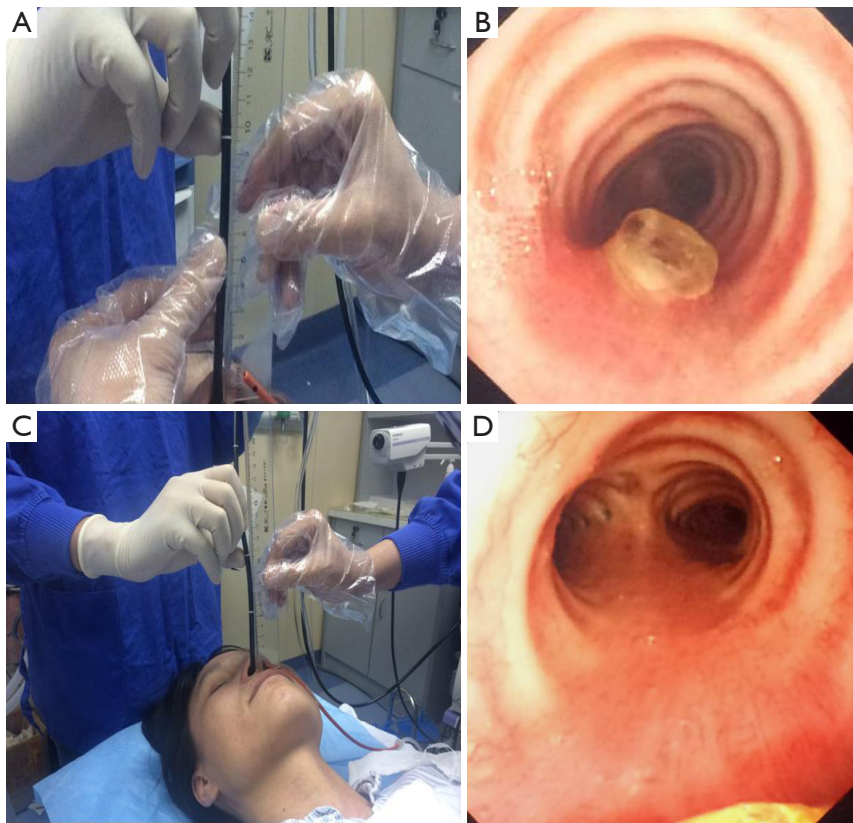
Figure 3 After bronchoscopic intervention, a second preoperative bronchoscopy showed that most of the primary tumor had been resected, and the residual tumor had invaded the posterior wall of trachea. The distal and proximal ends of the residual tumor and the surgical resection range were evaluated again.
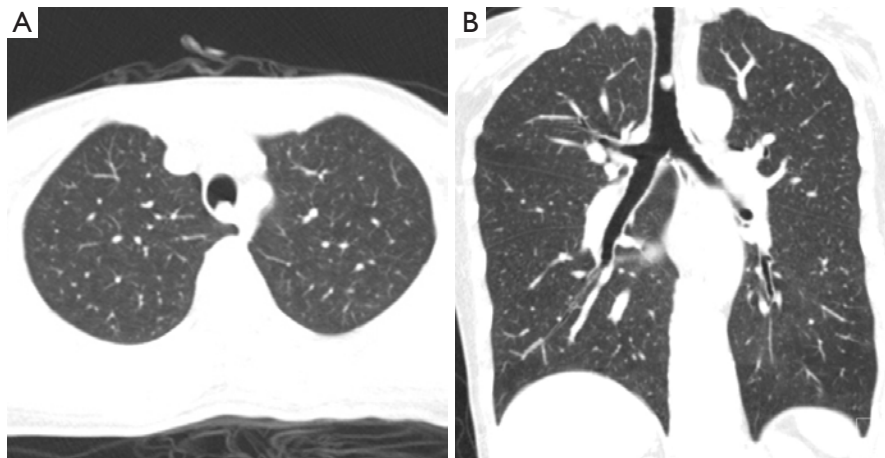
Figure 4 A second postoperative chest computed tomography (CT) following bronchoscopic electrocautery indicated that the residual tumor was located in the mid-lower section of the trachea and 6 cm away from the carina. It had invaded the entire posterior wall of trachea, and the posterior wall of trachea was remarkably thickened.

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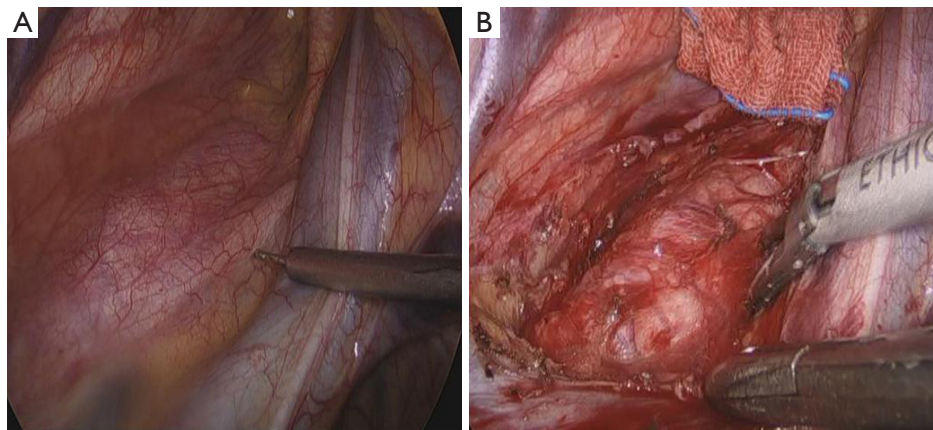
Figure 5 Nerve blockage and surgical process. (A) Right thoracic vagus blocks were performed before surgery; (B) cut open the mediastinal pleura to dissociate the thoracic trachea.

Anesthesia

Epidural anesthesia was applied in this patient. After local anesthesia, a thoracic epidural catheter was inserted into the T7/8 intercostal space, via which 2 mL of 2% lidocaine was slowly injected for testing the anesthetic effectiveness. After the testing, 3 mL of 0.5% ropivacaine was injected into the catheter. Sufentanil (10 µg) and propofol (80 mg) were used during the induction of anesthesia. During the surgery, anesthesia was maintained using remifentanil (0.03–0.05 µg/kg per min) and propofol (0.2 mg/kg per min). Also, 40% oxygen was delivered using a laryngeal mask at a rate of 3.5 mL/min. Spontaneous breathing was maintained throughout the surgery. The depth of anesthesia was measured using the EEG bispectral index during the surgery. Finally, devices for tracheal intubation, VATS endobronchial intubation, and mechanical ventilation were also prepared to prevent emergency situation (e.g., airway obstruction) and ensure the surgical safety.

Surgical process

The patient was placed in a left lateral decubitus position. A 1-cm observation port was made in the 6th intercostal space at right anterior axillary line for the placement of 30° thoracoscopy. In addition, two incisions (2 cm and 0.5 cm in length, respectively) were made in the 3rd intercostal space at anterior axillary line and in the 7th intercostal space at posterior axillary line as the operation ports. Intercostal nerve block (from the second intercostal space to the seventh intercostal space) using 1% lidocaine was performed; meanwhile, 2 mL of 0.5% bupivacaine was used

for vagus nerve block (*Figure 5A*). During the surgery, we found that the collapse of the operated lung was good; then, the lung was lifted forwards to achieve good surgical field. The trachea section from the level of suprasternal notch to the level of carina was separated (*Figures 5-8*), and the mass borders and the resection scope were further confirmed using bronchofiberscopy during the surgery. The tracheal mass was completely removed about 1.0 cm away from the outer margin of the tumor (*Figures 9,10*). Intra-operative frozen section analysis showed that the surgical margin was negative. After the reconstruction of the tracheal stump by continuous suture using 2–0 Prolene sutures, we carried out anastomotic leak test using sterile saline (*Figures 11-15*). After it was confirmed that there was no anastomotic leak or intrathoracic active bleeding, we closed the chest incisions, while two chest tubes (up and down) were remained in the thoracic cavity for drainage. The anesthesia time and surgery time were 105 minutes and 180 minutes, respectively. The intraoperative blood loss was controlled within 30 mL, and the intraoperative SpO$_2$ was maintained between 97–100%. Blood gas analysis showed that the patient had no non-respiratory acidosis. The intraoperative EtCO$_2$ was between 40 and 48 mmHg. The patient's vital signs remained stable throughout the operation.

Under non-intubated anesthesia with spontaneous breathing, the procedure was performed on July 8th 2015 (*Figure 16*).

Postoperative outcome

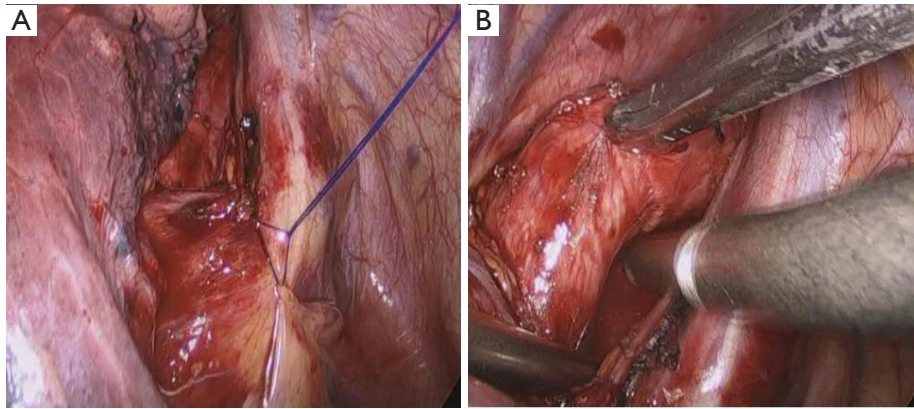Postoperative chest X-ray showed that the operated

Figure 6 Suspension of thoracic vagus nerve to protect the nerve; dissociate the tissues behind the thoracic trachea.
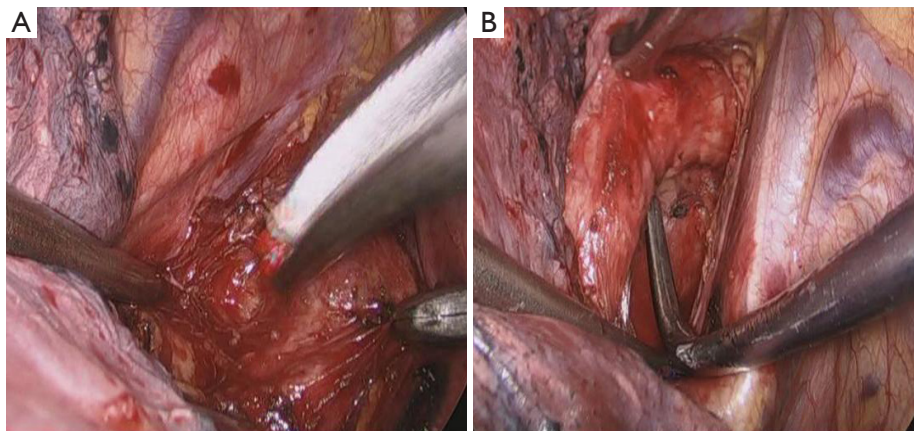

Figure 7 Blunt dissociation of the posterior segment of trachea; dissociate the thoracic trachea using right-angled forceps.
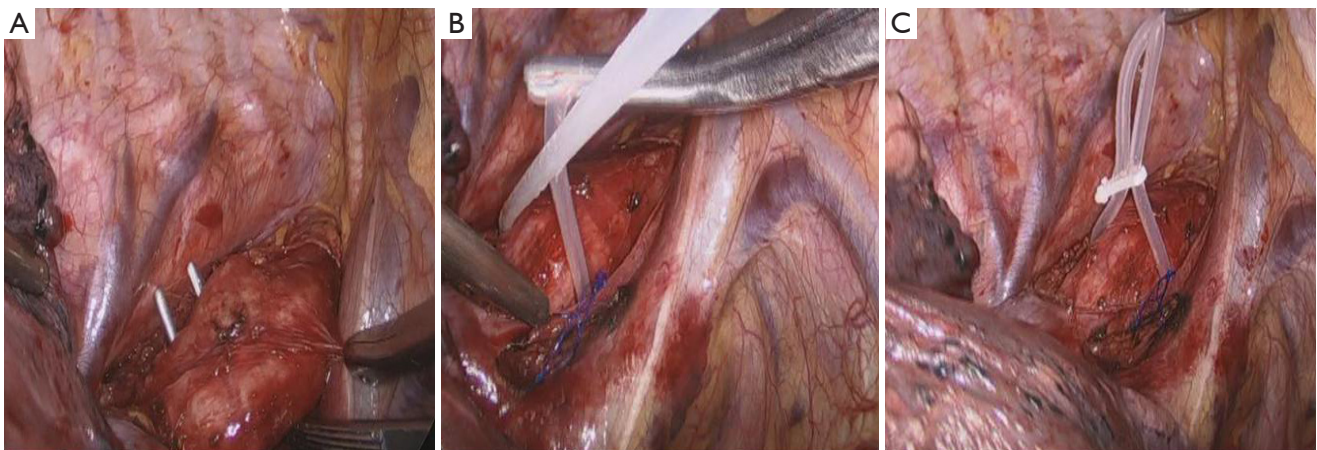

Figure 8 Dissociate the thoracic trachea using right-angled forceps; suspend the dissociated thoracic trachea using a retraction cord.
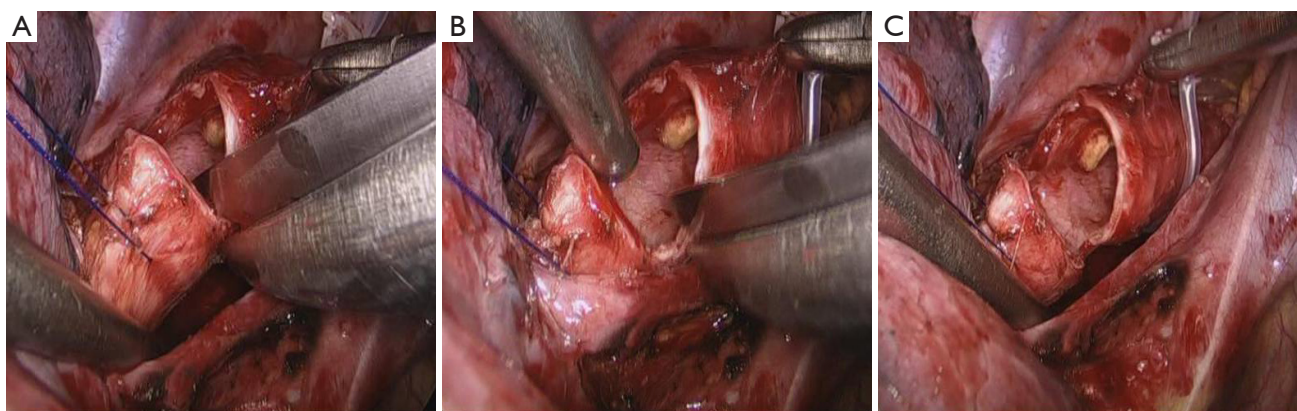
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Figure 9 Divide at the distal end of tracheal mass and at the distal end of tracheal ring.
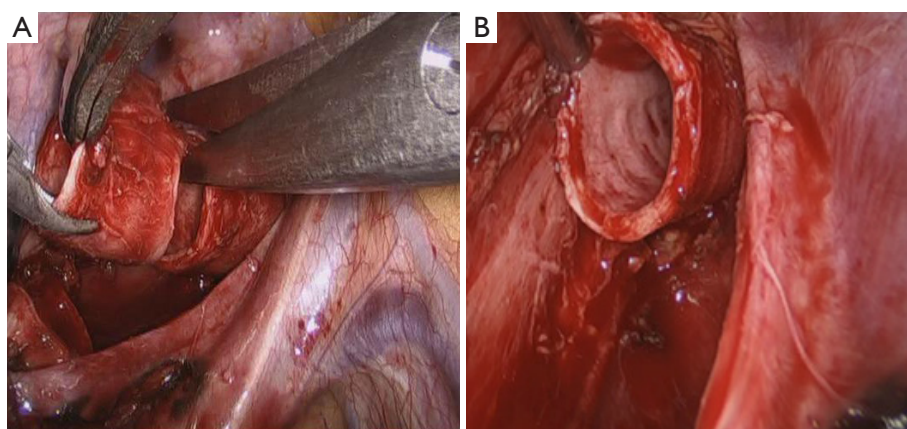
Figure 10 Divide at the distal end 1cm away from the lower edge of the mass.

lung was well re-expanded and there was no sign of pneumothorax. The patient had no postoperative symptoms such as nausea and vomiting but complained of mild pain at the chest tube insertion site. Non-steroidal anti-inflammatory drugs and ambroxol were administered to alleviate the symptom. The patient began to eat and drink 6 hours after surgery. She was able to walk slowly 10 hours after surgery. The patient did not experience any surgery-related complication. The chest tubes were withdrawn on the second postoperative day, and the patient was discharged on the fifth postoperative day. During the 3-month follow-up, the patient had good general conditions and did not complain of any respiratory symptom.

Postoperative diagnosis

The mass was pathologically diagnosed as intermediate-grade mucoepidermoid carcinoma of the trachea invading the bronchial wall. The mass was sized 1.2 cm × 1.0 cm × 0.6 cm, and it had protruded into the tracheal lumen (*Figure 17*).

Immunohistochemical findings: CK7 (+), Napsin A (–), TTF1 (–), Calponin (–), P63 (–), CK5/6 (–), P40 (–), and Ki67 (about 15%).

Special staining: Mayer's dyeing (+).

Genetic testing: EGFR exon 19 deletion.

Discussion

According to our experiences, VATS procedures in non-intubated patients with spontaneous breathing have many advantages: first, the anesthesia effectiveness of this procedure is similar to the traditional anesthesia. The anesthesia depth and vital signs were maintained stably throughout the surgery, and the patient did not wake up
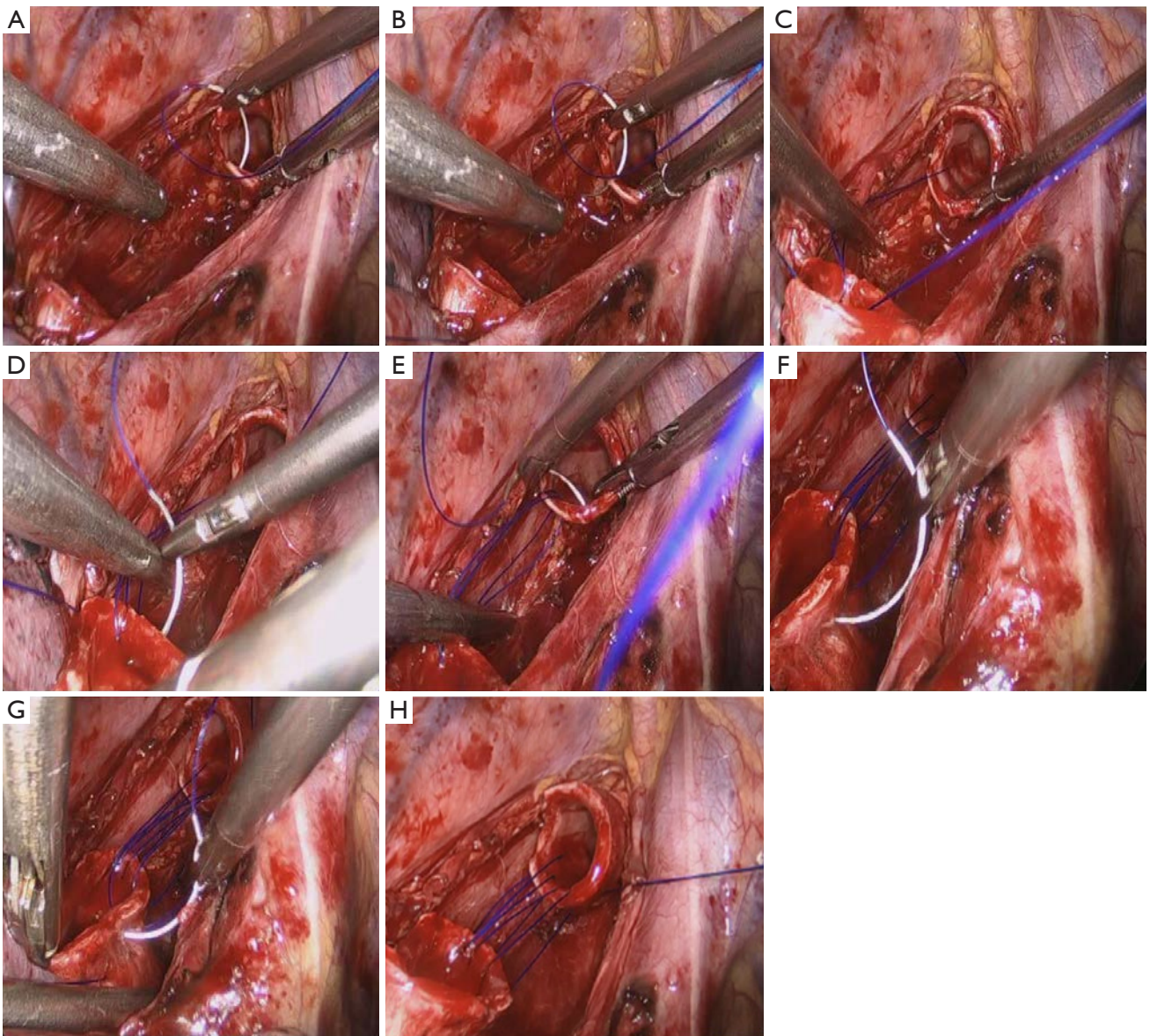
Figure 11 After the tumor was resected, the posterior wall of the trachea was continuously closed using the Prolene sutures.
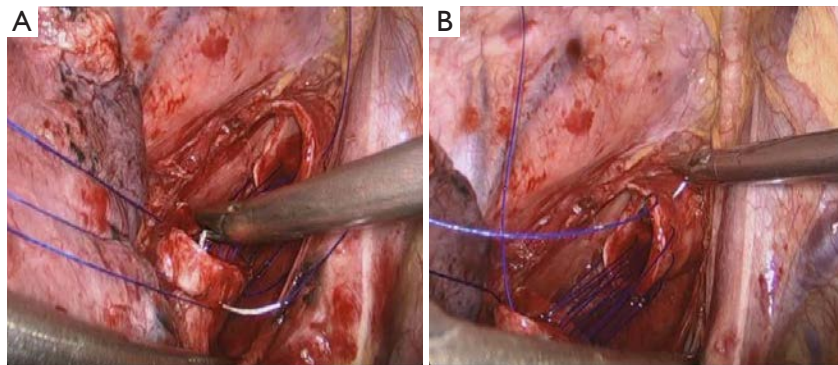

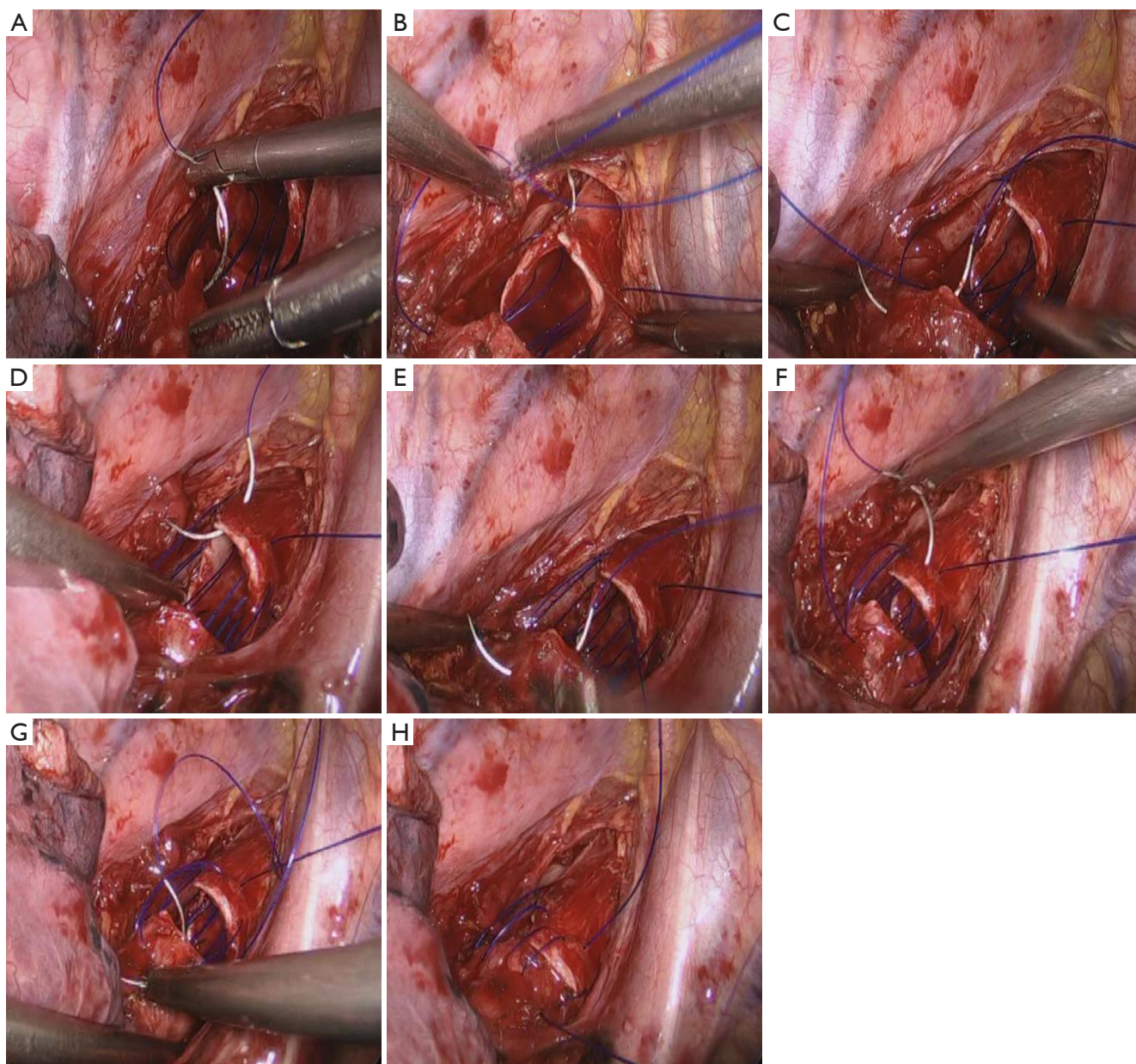**Figure 12** The lateral wall of the trachea was continuously closed using the Prolene sutures.

Figure 13 The anterior wall of the trachea was continuously closed using the Prolene sutures.

during surgery. Second, no muscle relaxant is required during the anesthesia, thus avoiding the slow recovery of lung function and its relevant airway complications due to the use of muscle relaxant. In addition, inflammatory cytokines such as TNF-α can increase the permeability of the blood vessels and cause tissue edema. As shown in our previous study, the inflammatory cytokine levels were significantly lower in non-intubated patients than in intubated patients (7).

In our current case, the non-intubation technique under spontaneous breathing brought more benefits to the patient: it decreased the risk of hemorrhage and airway edema following tracheal intubation; meanwhile, the trachea had larger range of motion and the surgical field was clearer in the absence of tracheal intubation. Spontaneous breathing during surgery helped to maintain good hemodynamic status and blood oxygen saturation.

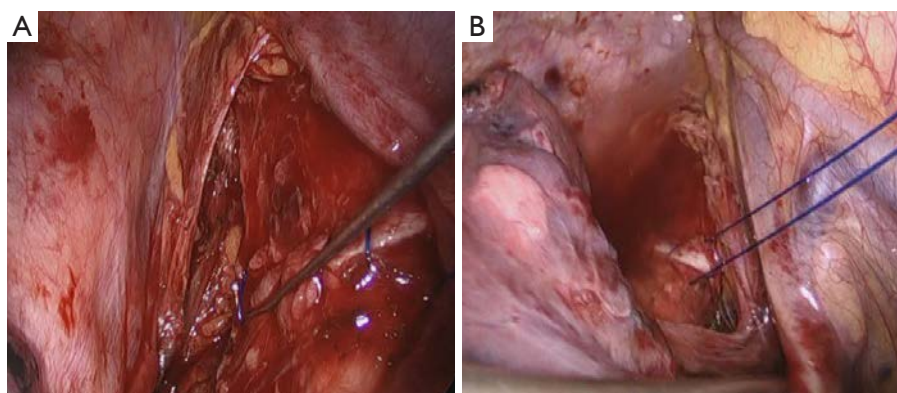However, not all patients are suitable for non-intubated

Figure 14 The sutures were retracted stepwise using a nerve hook to tighten the anastomosis, reduce tension, and prevent the sutures to cut the anastomosis.
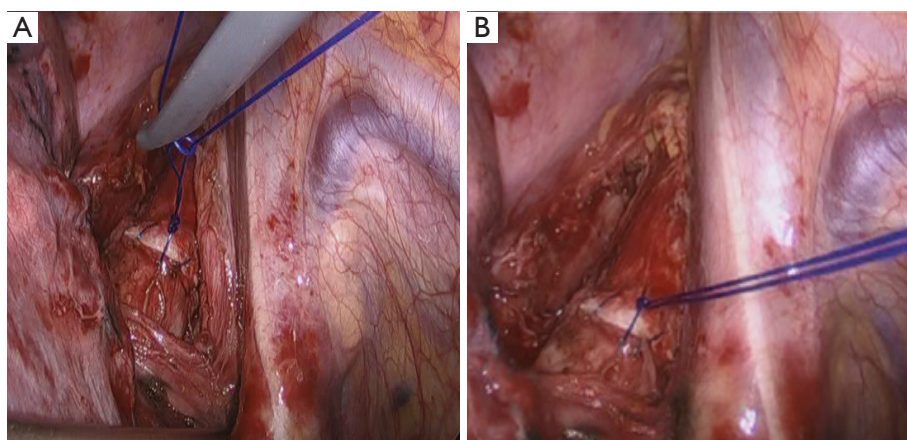

Figure 15 Anastomotic leak testing; knots were tied and fixed after the anastomosis was confirmed to be leak-free.

Figure 16 VATS resection of a tracheal mass and reconstruction of trachea under non-intubated anesthesia with spontaneous (6). VATS, video-assisted transthoracic surgery.
Available online: http://www.asvide.com/articles/910

anesthesia under spontaneous breathing. This technique should be avoided in patients with the following conditions for safety considerations: (I) low blood volume, hemodynamic instability, or dysfunction of blood coagulation; (II) American Society of Anesthesiologists (ASA) score >3; (III) heart failure, abnormal anatomical structures, or spinal cord and peripheral nerve diseases; (IV) pulmonary insufficiency (FEV1 <60% expected value) and/or poorly controlled asthma; (V) severe pleural adhesions; (VI) BMI >25 kg/m^2; and (VII) low cardiac output due to aortic stenosis, hypertrophic cardiomyopathy, severe arrhythmia, mitral stenosis, or complete atrioventricular block. Meanwhile, devices for endotracheal intubation, thoracoscopic intubation, and mechanical ventilation should also be prepared during the
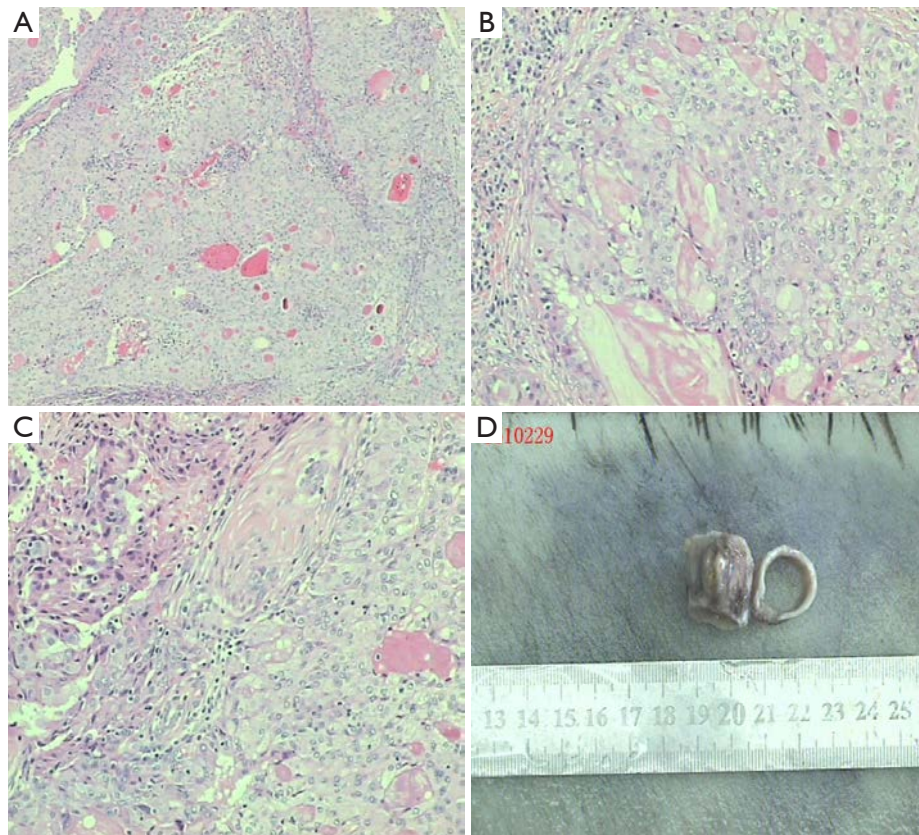
Figure 17 Pathology result: two parts inside the bronchus: 1.5 cm in length and 1.8 cm in diameter; and 0.6 cm in length and 1.5 cm in diameter. A 1.2 cm × 1.0 cm × 0.6 cm mass could be seen on the surface. The mass protruded into the tracheal lumen, with gray-yellow cutting surface and moderate texture (magnification, ×100).

surgery to ensure the safety of patients. Active intervention along with endotracheal intubation or thoracoscopic intubation should be performed in case the following conditions occur during the surgery: (I) the SpO_2 cannot be maintained above 90%; (II) obvious carbon dioxide retention, along with the development of respiratory acidosis; and (III) sudden bleeding that cannot be stopped quickly (7).

In this article we described the application of VATS resection of a mass and reconstruction of trachea in a non-intubated patient with spontaneous breathing. As shown by the surgical outcomes and intraoperative conditions, this anesthesia and surgical technique is feasible for patients who are unsuitable for tracheal intubation. However, the surgical team must have rich experiences in non-intubated anesthesia with spontaneous breathing and are able to properly deal with surgery-related complications.

Acknowledgements

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Totally robotic-assisted non-circumferential tracheal resection and anastomosis for leiomyoma in an elderly female

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Abstract: We describe a novel technique of totally robotic-assisted non-circumferential tracheal resection and running anastomosis with coverage of anastomosis with anterior mediastinal fat flap. A 71-year-old female presented with cough and CT scan revealed a mass at the intra-thoracic trachea. A complete robotic-assisted tracheal resection and anastomosis was performed. The postoperative course was uneventful. The final pathologic examination confirmed the diagnosis of primary tracheal leiomyoma.

Keywords: Tracheal tumor; robotics; minimally invasive surgery

Introduction

Primary tracheal leiomyoma is a rare benign tumor arising from the smooth muscle cells of the membranous portion of the trachea, which account for approximately 1-2% of all primary tracheal tumors (1,2). Because these lesions are so rare, the optimal management approach has not been defined. Historically, a tracheal sleeve resection has been considered to be the standard treatment. Here, we present a novel robotic minimally invasive technique for performing a non-circumstantial tracheal resection that minimizes the possible operative risk. To our knowledge, it is the first report of robotic-assisted tracheal resection in an elderly female who had experienced recurrence cough and receive a diagnosis of an intra-thoracic tracheal leiomyoma.

Operative techniques

A 71-year-old female with cough was referred to our hospital. Computed tomography revealed an intraluminal tracheal mass arising from the membranous portion of the trachea with 5 cm distal to the vocal cords and 4 cm proximal to the carina (*Figure 1A*). A flexible bronchoscopy demonstrated a wide-based submucosal tumor (*Figure 1B*).

Pathologic examination of the specimen obtained during bronchoscopic biopsy revealed uncharacteristic hyperplasia of squamous epithelium with karyokinesis. On admission, routine laboratory studies including pulmonary function tests were the normal. The management options were outlined to the patient, including regular surveillance bronchoscopy, immediate bronchoscopic local excision or tracheal resection. The patient chose the latter and underwent a robotic-assisted operation.

The patient was placed in a left lateral decubitus position and double-lumen intubation was installed. Three-arm robotic system was used (*Figure 2*). The first port was placed in the seventh inter-costal space on the midaxillary line for the camera (0°). The second port was made in the seventh inter-costal space in the posterior axillary line (one robotic arm), and the third port was made in the fifth inter-costal space in the anterior axillary line for the other robotic arm. An additional small incision, 2 cm long, was made in the third intercostal space in the anterior position just between latissimus dorsi and pectoralis major for the assistant surgeon to insert conventional instrument and was used pulled down lung tissue in order to get good exposure. The dissection of the trachea and other structures were robotically performed with the two arms. No CO_2
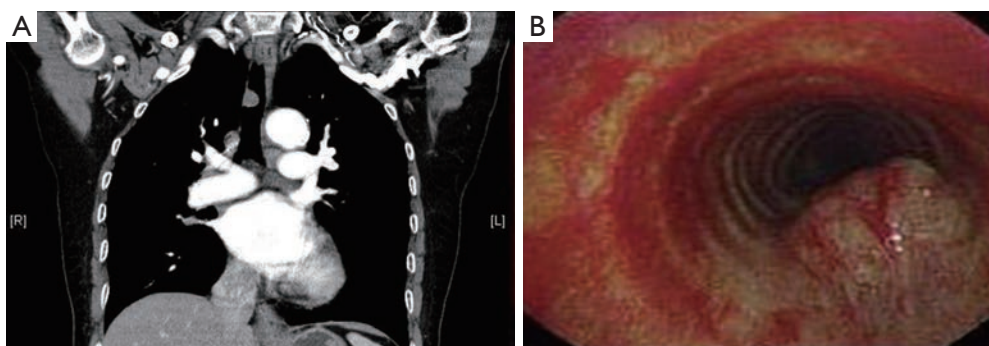
Figure 1 (A) Coronal computed tomography showed a mass in the intra-thoracic trachea; (B) the flexible bronchoscopy showed the tracheal tumor.

Figure 2 (A) The incisions' distribution for robotic tracheal resection; (B) photograph of the gross pathologic specimen; (C) computed tomography showed no stenosis on 14th day postoperative.

insufflation was utilized.

The first action is to retract the lung down by orbicular-ovate grasping forceps via the additional small incision. The azygous vein was transected and clamped with hemlock. Cautious dissection minimized risk of damage to the recurrent laryngeal nerves. The trachea was dissected and the mass of the trachea was completely exposed (*Figure 3A*).

The tracheal wall in the distal and proximal of the mass was firstly sutured for suspension. Complete excision of the mass and the partial trachea was performed (*Figure 2B*). The area of deletion of the tracheal wall was about 2.5 cm × 2 cm (*Figure 3B*). Intraoperative frozen examination revealed a benign spindle cell carcinoma with tumor-free surgical margins.

The reconstruction was made by anastomosis with running sutures. The cartilaginous portion and the membrane portion of the trachea were sutured with two 2-0 Prolene sutures (*Figure 3C*). The robotic clamp and needle holder were used to tie the suture knots following

the anastomosis (*Figure 3D*). The fat flap of anterior mediastinum was used as the coverage of anastomosis because of a light air leakage from the eye of a needle. Two chin stitches were placed in order to get cervical flexion and avoid tension of tracheal anastomosis after operation.

Intraoperative blood loss was 100 mL and operative time was 120 minutes. The postoperative course was uneventful. The chest tube was removed on postoperative day 3. The patient was discharged on postoperative day 9. The final pathologic examination confirmed the diagnosis of primary tracheal leiomyoma with tumor-free surgical margins. Computed tomography showed no stenosis in the intra-thoracic trachea on 10th day postoperative (*Figure 2C*).

Comments

Primary tracheal leiomyomas are very rare tumors and these benign tumors arise from the smooth muscle cells of the membranous portion of the trachea and have the
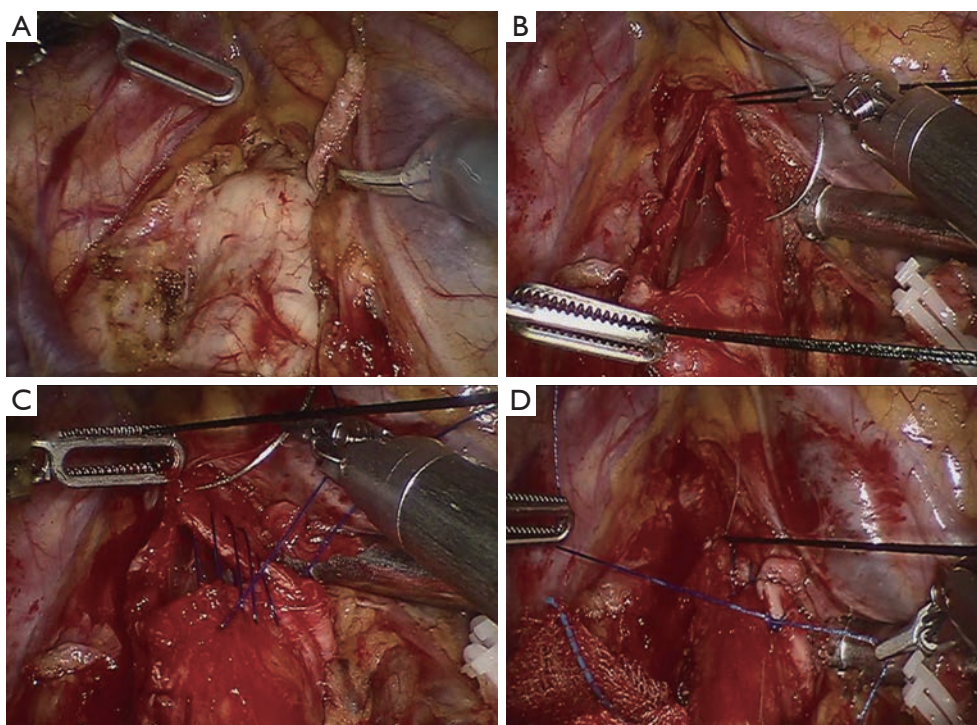
Figure 3 (A) The intra-thoracic trachea was dissected and the mass was exposed; (B) complete excision of the mass and the partial trachea was performed. The area of deletion of the tracheal wall was about 2.5 cm × 2 cm; (C) the cartilaginous portion and the membrane portion of the trachea were sutured with two 2-0 Prolene sutures; (D) the robotic clamp and needle holder were used to tie the suture knots following the anastomosis.

potential to cause tracheal obstruction(3,4). Endotracheal leiomyoma is commonly associated with symptoms, which are manifested as a chronic cough, sputum, dyspnea, stridor, and fever due to obstructive pneumonia (5). Large tracheal tumors can even cause obstruction of the main airway, resulting in symptoms of asphyxia. These conditions are the main reasons for resection of this benign tumor. In our case, the lesion presented as a wide-based soft tissue mass filling the thoracic tracheal lumen.

Bronchoscopic, local surgical excision and partial tracheal resection have all been described. However, in cases of a wide-based tumor, bronchoscopic intervention may result in incomplete resection or recurrence, so surgical resection has still been the standard treatment for these lesions (5). Decisions about the operative strategies for a tracheal tumor should depend on the size, location, width of the base of the lesions, local invasion of the lesion, experience of the surgeon, and diverse accompanying conditions. And benign and low-grade malignant tumors should be resected conservatively with preservation of lung parenchyma (6).

Robotic-assisted surgical technologies have been

adopted rapidly since US Food and Drug Administration (FDA) approval in 2000. In the early experience with robotic surgery, studies comparing robotic lobectomy to thoracoscopic lobectomy have found no significant clinical benefit (7). The robotic platform, with its wristed instruments providing articulated movements, is designed to mimic open surgery and facilitates the adoption of minimally invasive techniques. To date, the thoracoscopic or robotic approaches are seldom used to tracheal resection. This is the first report of successful robotic-assisted lateral wall resection of the trachea for leiomyoma. During the operation, by using robotic two-arm, the tracheal resection and anastomosis can be completed easily in a manner similar to the traditional open approach with skills and experience obtained from our previously performing complex robotic thoracic procedures.

Moreover, in the most studies available on tracheal resection, interrupted suture is used for tracheal anastomosis. However, according to our previous experiences and other reports, the technique of running suture is safe and feasible during tracheal anastomosis (8). So the anastomosis was

carried out using running Prolene stitches. Because a light air leakage from the eye of a needle was found, the fat flap of anterior mediastinum was used to fix the anastomosis.

In conclusion, we consider that the robotic-assisted surgical procedure described here is simple, feasible, and as effective as the open surgery, with good clinical outcomes and better cosmetic results. This method may present a new alternative strategy for treating benign tumor of the trachea.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Operative endoscopy of the airway

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Abstract: Airway endoscopy has long been an important and useful tool in the management of thoracic diseases. As thoracic specialists have gained experience with both flexible and rigid bronchoscopic techniques, the technology has continued to evolve so that bronchoscopy is currently the foundation for diagnosis and treatment of many thoracic ailments. Airway endoscopy plays a significant role in the biopsy of tumors within the airways, mediastinum, and lung parenchyma. Endoscopic methods have been developed to treat benign and malignant airway stenoses and tracheomalacia. And more recently, techniques have been conceived to treat end-stage emphysema and prolonged air leaks in select patients. This review describes the abundant uses of airway endoscopy, as well as technical considerations and limitations of the current technologies.

Keywords: Endoscopy; bronchoscopy; endobronchial therapy; therapeutic bronchoscopy; interventional bronchoscopy

Introduction

Since its first description in 1897 (1), when Gustav Killian bronchoscopically extracted a piece of bone from the airway of a patient, bronchoscopy has undergone extensive evolution and currently resides as one of the thoracic surgeons' most important and useful tools. Endoscopy of the airway affords the surgeon multiple diagnostic and therapeutic options for a variety of disease states. This review describes the various current uses, equipment, and technical considerations for surgical airway endoscopy.

Equipment

The most fundamental instruments needed for airway endoscopy are a bronchoscope and a light source. Both rigid and flexible bronchoscopes are widely available for use by the thoracic surgeon. Each has distinct advantages and disadvantages and the preferred approach is generally dictated by the procedural goals, but often both techniques

are used in conjunction. It is therefore imperative that the thoracic surgeon develops a level of comfort with both flexible and rigid bronchoscopic methods to achieve optimal outcomes.

Flexible bronchoscopy is performed using a small caliber endoscope, which can be inserted nasally or orally, in the awake or anesthetized patient. The flexible bronchoscope offers excellent visualization of the proximal and distal airways and contains a working port, which can accommodate a variety of instruments that can be used for diagnostic and therapeutic purposes. Flexible bronchoscopy is generally well tolerated, which makes it useful when multiple repeated interventions are required. The learning curve for flexible bronchoscopy is fairly shallow and, therefore, many practitioners easily develop a level of comfort with its use.

Rigid bronchoscopy, in contrast, is more technically demanding to master, but affords the bronchoscopist many more diagnostic and therapeutic options. However, it does require an anesthetized patient and demands

experience with airway intubation, as insertion of the rigid bronchoscope may be technically challenging when anatomical challenges exist. Therefore, preoperative assessment is important. History should include inquiry regarding neck and cervical spine issues, and physical examination should assess for neck mobility, body habitus, and airway quality.

Anesthesia

Communication between the anesthesia and surgical teams is absolutely critical when undertaking any airway procedure; there is probably no other surgical procedure that requires more coordination of anesthesiologist and surgeon than co-management of a threatened airway. Prior to induction of anesthesia, it is important to conduct a preoperative "timeout" with the surgical, anesthesia, and nursing teams to discuss the operative plan, specific patient anatomy, and ensure all necessary equipment are available and operational. The surgeon is at the bedside when the patient is induced and is prepared to establish emergent airway access with a rigid bronchoscope if necessary, as deep anesthesia may lead to loss of a patent airway. This is particularly important in the case of any obstructive airway lesion.

When rigid bronchoscopy is indicated, a totally intravenous general anesthesia is preferred with deferral of paralysis until the surgeon and anesthesiologist are mutually in agreement that a stable airway is achieved or achievable. There are a variety of ventilatory approaches that have been well described, including spontaneous assisted ventilation (2), jet ventilation (3), apneic ventilation (4), and closed system ventilation. In most cases the simplest and most reliable is standard closed system ventilation, treating the rigid bronchoscope as an endotracheal tube, with pauses in ventilation when the bronchoscope is opened for suctioning, biopsy, or stent placement. Although jet ventilation is popular, it is an unnecessary encumbrance to the procedure and adds noise and aerosolized blood and secretions that are annoying to the operator and team. Limiting the fraction of delivered oxygen to less than 50% is often necessary, particularly when utilizing the neodymium-doped yttrium aluminium garnet (Nd:YAG) laser or electrocautery to prevent combustion.

Procedural basics

Insertion of the flexible bronchoscope is rarely demanding and can be accomplished via nasal and oral routes.

Local anesthesia is paramount and there are a variety of approaches to achieve an adequate level of patient tolerance. When using a trans-nasal approach in an awake patient, it is useful to anesthetize the nasal passages with topical lidocaine jelly or 10% liquid cocaine, which mitigates much of the discomfort attributed to insertion of the bronchoscope. Aerosolized 4% lidocaine can be administered transorally with an atomizer. After insertion of the bronchoscope, the vocal cords are observed and anesthetized under direct visualization with topical injectable lidocaine. Depending on level of stimulation and patient tolerance, it is often useful to anesthetize the carina and distal airways as well to avoid coughing during the procedure.

The rigid bronchoscope is significantly more challenging to insert, but having a comfort with endotracheal intubation, a reliable plan, and an understanding of alternate methods will lead to a high degree of success. There are several described methods for rigid scope insertion, including use of a laryngoscope to directly visualize the vocal cords, or following the pathway of the endotracheal tube in an already intubated patient. The most straightforward technique is to directly intubate the trachea using the rigid bronchoscope, using the scope to identify the vocal cords, and directly pass through them in order to establish a bronchoscopically controlled airway. Positioning of the patient varies depending on several patient factors (e.g., age, obesity, anatomy), and either flexion or extension of the neck may be beneficial in different circumstances. In general, the best position for the initial intubation is similar to that used by the anesthesiologists for intubation, i.e. the neck flexed and chin pulled back, the so-called "sniffing position". Once intubated however, it is often easier to access the lower airways with a change of this position into one of neck extension to more easily align the upper and lower airway. For intubation, the endoscopist stands directly above the patient's head and, after the patient is preoxygenated, a soft guard is placed on the upper teeth. The endotracheal tube or laryngeal mask airway (LMA) is withdrawn and the rigid bronchoscope is inserted orally with the right hand, while the left hand stabilizes the scope and protects against leverage on the teeth at the level of the patient's mouth. The rigid scope is carefully inserted along the posterior aspect of the tongue, then, gently lifting upward, the epiglottis is brought into view and the scope used to elevate the epiglottis. This allows visualization of the vocal cords, which are intubated after rotating the bronchoscope 90 degrees and inserting the leading beveled edge to limit trauma to the vocal cords. A common error is

Table 1 Causes of benign and malignant airway obstruction

Benign
  Post-intubation
  Post-tracheostomy
  Anastomotic stricture (lung transplant, sleeve resection, airway resection)
  Intrinsic airway tumors
  Extrinsic airway tumors
  Inflammatory
  Infectious
  Foreign body
Malignant
  Adjacent malignancies
    Lung cancer
    Thyroid cancer
    Esophageal cancer
    Mediastinal tumors
  Primary airway tumors
    Carcinoid tumor
    Adenoid cystic carcinoma
    Mucoepidermoid carcinoma
    Squamous cell carcinoma
  Metastatic tumors
    Breast cancer
    Renal cell carcinoma
    Melanoma
    Colorectal
    Other

extending the scope too far under the epiglottis and actually passing the arytenoids, lifting the larynx, and visualizing the esophagus rather than the vocal cords (yet this modification is exactly how to perform rigid esophagoscopy). If insertion is challenging, the patient is re-oxygenated and the oropharynx is suctioned clean before additional attempts at intubation are made. Occasionally repositioning the patient, adding a shoulder roll, or using an alternate method of intubation is necessary.

After successful insertion of the rigid bronchoscope, ventilation is initiated and the airway anatomy is assessed. The next section of this review highlights some of the most common diagnostic and therapeutic uses of airway endoscopy and describes the technical aspects and limitations of these techniques.

Airway obstruction

Stenosis

Often, airway obstruction is an urgent or emergent predicament and requires a thoughtful and sometimes rapid approach to restore airway patency. Emergency surgical management is rarely indicated, as endoscopy is nearly always able to stabilize and temporarily palliate both benign and malignant sources of airway obstruction and can often provide both temporizing and definitive treatment.

Benign stenoses are frequently iatrogenic, occurring after prolonged intubation, tracheostomy, lung transplantation, tracheal resection, and sleeve resection, but can also be caused by extrinsic compression, rare benign tumors, infectious/inflammatory processes, or foreign bodies (*Table 1*). Malignant stenoses have a variety of etiologies related to primary airway tumors, adjacent cancers invading or compressing the airway, and metastatic disease. Just as there are a variety of etiologies of airway stenoses, there are numerous endoscopic techniques to treat them. To achieve consistent and durable results, it is essential for the thoracic surgeon to be familiar with a full repertoire of techniques, described below.

Balloon dilation was first described in 1984 (5) and has evolved into a highly useful technique for relief of benign, and some malignant, airway stenoses. The significant advantages of balloon catheter dilation are the deliverability through the flexible bronchoscope, ease of use, control of the dilation diameter, and the ability to perform as an outpatient procedure. The major limitation is durability, which is variable, and often necessitates frequent repeat dilations. Fortunately, repeated balloon dilation, particularly using flexible bronchoscopy, is well tolerated and, depending on the underlying etiology, can occasionally achieve prolonged period of airway patency. Dilation is safe and severe complications are extremely rare, but overdilation may cause airway laceration and hemorrhage and in some cases airway rupture or even pulmonary artery injury (6-8). Success of balloon dilation is most often seen in patients with short-segment fibrotic stenoses and in these patients, immediate relief of symptoms is observed while the patient is in the post-anesthesia care unit. While dilation has been described in non-anesthetized patients, the use of general anesthesia reduces pain and allows easy transition to other techniques if necessary. Patients with idiopathic laryngotracheal stenosis often can have prolonged periods of palliation (12–24 months) that avoids or delays the need for surgical reconstruction. However, post-intubation

stenoses are usually palliated only briefly (days to weeks) and dilation simply serves for airway stabilization and semi-elective planning for tracheal resection and reconstruction. Paradoxically, post-tracheostomy stomal stenoses rarely benefit from dilatation, usually because the membranous wall is uninvolved and highly compliant, meaning that the dilatation only expands the normal membranous wall that recoils back to its normal position as soon as the dilation is completed. Finally, extrinsic airway compression is rarely improved by dilatation alone, usually requiring endoluminal stenting to establish stable palliation.

The incidence of bronchial stenosis after lung transplantation has been reported to be approximately 8% (9,10). Often this is discovered in the first couple months after transplantation. For patients who develop early anastomotic stricture after lung transplantation, the timing of therapeutic intervention is important. It is preferable to delay intervention until 6 weeks after the initial operation, if possible, to allow for anastomotic maturity and integrity. Treatment often requires debridement of granulation tissue combined with balloon dilation, which often needs to be repeated at 1–4 weeks intervals depending on the severity of the obstruction and the patient's symptoms. Stenting may also be appropriate in some patients (described in more detail below). Similar principles apply to other airway anastomotic strictures, e.g., those after tracheal resection or sleeve lobectomy. However, individualization is important to assure a stable airway and distal airway continuity.

Endobronchial tumors

Endobronchial tumors are uncommon, but when they occur they are a common cause of airway obstruction. Pathologies include primary airway tumors, such as adenoid cystic carcinoma and squamous cell carcinoma in the trachea and carina, or carcinoid tumors in central airways below the carina. Mechanical tumor core out is useful for initial management of both benign and malignant tumors, particularly in patients who are not candidates for surgical resection, or those who present with a threatened airway or post-obstructive symptoms that need management prior to definitive resection. For example, core-out of an endoluminal tumor is a valuable strategy for patients with obstruction resulting from carcinoid tumors, which allows for both a definitive biopsy, as well as clearance of obstructive pneumonitis along with better definition of tumor margins prior to a possible sleeve resection. Core out may be accomplished using either flexible or rigid bronchoscopic techniques. However, rigid bronchoscopy is significantly superior to flexible techniques because of its simplicity, speed, versatility and the surgeon's ability to apply a variety of techniques via the rigid bronchoscope in order to restore airway patency. In addition, should bleeding arise during the core out procedure, the rigid bronchoscope is a much more effective means to aspirate blood and obtain hemostasis. The rigid scope can readily compress bleeding mucosa, allows for delivery of larger caliber suction devices to improve visualization, and use of other modalities to achieve hemostasis.

The method most useful for tumor core out begins with insertion of the rigid bronchoscope and complete visualization the tumor, its pedicle, and the distal airway to delineate the full extent of tumor involvement. The tumor pedicle is then engaged with the tip of the rigid endoscope, which frequently easily dislodges the tumor, and the tumor fragment is removed and debridement completed with biopsy forceps. If bleeding occurs, it generally stops spontaneously, but on occasion compression using the scope or application of topical dilute epinephrine may be a useful adjunct. In rare cases of more severe hemorrhage, electrocautery or Nd:YAG laser application may be an effective means of hemostasis. Historically, it was considered a contraindication to endoscopically biopsy carcinoids and other well-vascularized tumors for fear of massive hemorrhage, but this has been disproven and even well vascularized tumors such as renal cell carcinomas can be safely cored out.

Adjunct techniques for airway obstruction

Laser

The Nd:YAG laser is a useful tool for select cases of airway obstruction. Laser vaporization is a helpful adjunct to mechanical core-out in cases of incomplete tumor debridement, when the location of the tumor is more distal or inaccessible, and also in cases of airway granulations. We employ the Nd:YAG laser with a power setting of 35 watts and a 0.5-s pulse duration for this purpose. As mentioned, the Nd:YAG laser can be useful to control bleeding after biopsy or tumor removal, but is rarely needed for this purpose.

Stenting

Stenting is a useful adjunct to many of the above techniques and in many cases achieves durable results, but stent complications are frequent. Frequently, airway stenting is performed because of surgical ineligibility due to inadequate physiological reserve in patients that might otherwise be

candidates for resection. Airway stenting is nearly always combined with other bronchoscopic modalities for treating the endoluminal lesion, which can include (I) core out and mechanical debridement; (II) airway dilation; (III) resection with different energy sources or cryotherapy; and (IV) endoluminal brachytherapy or photodynamic therapy. Stenting should be considered when there is persistent symptomatic airway narrowing after other interventions such as core-out or dilatation, typically when the diameter of an affected airway remains <50% of normal diameter. Stenting is usually the only endoluminal option for patients with extrinsic airway compression, long-segment inflammatory stenosis, or residual obstruction from endoluminal tumor.

Stenting of airway lesions requires a thorough understanding of the various advantages and disadvantages of the available airway endoprostheses. The ideal endoprosthesis is a stent that is (I) easily deployed and adjusted but does not readily migrate; (II) resists compressive forces yet does not erode or breach the native airway mucosa; (III) conforms to the airway contour without kinking or bending; (IV) elicits minimal foreign body reaction and prevents tissue ingrowth or granulation; and (V) allows mucociliary clearance to decrease mucous impaction. Unfortunately, the ideal airway endoprosthesis is not presently available. Current airway stents have some of these properties, but none have all.

There are basically two main categories of airway stents: solid silicone and expandable, and selections from both categories should be readily available for deployment in any given clinical scenario. The main advantages of silicone stents are that they are inexpensive to manufacture; once positioned they are easy to adjust and remove; and relatively well tolerated with minimal reactivity for granulation formation. These stents come in a variety of different diameters and lengths. The disadvantages of silicone stents are that they are stiff and more difficult to deploy, requiring general anesthesia, intubation, and skill with rigid bronchoscopy. However, a considerable amount of sheer force may be required to push the stent across a tight stenosis or stricture, which can traumatize the airway. There are times that silicone stents may not generate sufficient radial force for some strictures or extrinsic compression from tumor. They also do not seat well in malacic segments or conform to longer tortuous stenotic segments, and thus will commonly migrate from position causing itself airway obstruction. It is important to be aware that silicone stents can ignite with laser treatment, which often is used to treat airway granulation.

Expandable bare metal airway stents have a more favorable inner luminal to outer luminal diameter ratio than silicone stents, and are easier to deliver, using flexible bronchoscopy with or without fluoroscopy under topical or general anesthesia. Once delivered, these stents are extremely stable and there is low likelihood of dislodgment or migration. Expandable metal stents can generate considerable radial force which may be favored in fibrotic strictures. Uncovered metal stents theoretically allow mucosal neoepithelialization with the reported possibility to resume mucociliary clearance and also allow ventilation of lobar orifices across the open interstices. However, in reality this potential benefit is far overshadowed by tissue ingrowth and granulation through the interstices that frequently occurs due to the foreign body reaction to the stent. This often results in obstruction of the stent itself, yet once embedded in the airway wall the bare metal stents are extremely difficult to remove without causing significant secondary airway damage. Recurrent obstruction from tissue or tumor ingrowth through the metal interstices can require repeated debridement or even repeat stenting within the stent. Expandable stents also can exert considerable radial force, and therefore, may erode through the airway into adjacent structures and risk creating a possible life-threatening bronchovascular fistula. As a result of these known shortcomings and complications, the United States Food and Drug Administration (FDA) issued a warning that bare metal airway stents should be avoided in the management of benign airway stenosis.

The experience of airway interventionalists and the complications of bare expandable metal stents led to the development of 3rd generation covered expandable stents. These are easier to adjust and remove than uncovered stents. The Polyflex® self-expandable stent is composed of a polyester mesh with a silicone coating, while the Aero® stent consists of a metal nitinol framework covered completely with polyurethane.

We have observed a high rate (94%) of symptomatic improvement in patients with the use of stents to treat benign and malignant airway stenoses (11). In our series, 15% of patients required multiple stents for relief of the obstruction and 41% required multiple endoscopic procedures to maintain symptomatic improvement.

Microdebriders, photodynamic therapy, cryotherapy

There are a host of other methods that have been described to relieve airway stenosis, including electrocautery debridement, mechanical endobronchial microdebriders, photodynamic therapy, and cryosurgical techniques.

These methods have been described in the literature with variable results. Microdebriders were initially developed for use in otolaryngology, but have recently been applied to obstructing airway tumors. The microdebrider combines a rotating blade with a suction cannula and has proven to be an effective and low-risk means of tumor removal (12,13). Photodynamic therapy relies on the administration of a photosensitizing substance followed by the application of light at a specific wavelength to an endoluminal tumor. The result is tumor destruction and it has been shown to be an effective means of restoring airway patency (14). However, due to the post-procedure edema that develops, it should not be used in patients with high-grade obstruction. In addition, the patient must undergo repeat bronchoscopy in the days following the procedure to remove sloughed off tissue, which may itself lead to airway compromise, and systemic photosensitivity for several weeks is very limiting for patients. Cryoablation involves the use of a cryogen, most commonly nitrous oxide, to cause localized tissue necrosis and has shown to be as effective as other modalities in symptom relief, although durability is marginal (15).

Tracheomalacia

Patients are sometimes referred to thoracic surgeons with a diagnosis of tracheomalacia based on cross-sectional imaging, physical exam findings, or bronchoscopy assessment. However, cross sectional imaging cannot reliably confirm the diagnosis (16). When tracheomalacia is suspected, careful evaluation of the airway using flexible bronchoscopy in the awake, locally anesthetized patient is necessary for diagnosis. This allows for direct, dynamic visualization of the airway. When tracheomalacia is present, the endoscopist will visualize airway collapse generally in the anterior-posterior dimension. Asking the patient to forcibly exhale or cough will often accentuate these findings.

Endoscopic findings often do not support a diagnosis of tracheomalacia, and in these patients, other etiologies are sought for the patient's symptoms. Normal patients have some degree of antero-posterior collapse during forced expiratory maneuvers, and this is accentuated in patients with the small airway obstruction of asthma or COPD due to the increased expiratory effort and pressure differences in these pathologies. It is important to not over-diagnose tracheomalacia, although distinguishing it as a primary cause or incidental finding associated with dyspnea is often difficult and may warrant an empiric trial of stenting. If the diagnosis is confirmed, the preferred initial treatment is airway stenting. Stent choice depends on the extent of the affected airways. For isolated tracheomalacia, a tubular tracheal stent may be effective. When the tracheomalacia is in the distal trachea or extends beyond the level of the carina, a Y-stent (Dynamic™ Y stent, Boston Scientific, Marlborough, MA) should be used. It is important to directly visualize the takeoff of the right upper bronchus and ensure that the stent does not cover this orifice. It is usually necessary to trim the right mainstem portion of the y-stent, on the lateral aspect to maintain patency of the right upper lobe bronchus. Silicone stents have been shown to have excellent short- and even long-term success in treatment of tracheomalacia, although numerous complications such as stent migration, infection, and obstruction have been described (17,18).

Advanced diagnostic techniques

Patients who present with non-small cell lung cancer (NSCLC) and other pulmonary or mediastinal masses often require tissue biopsy for diagnosis and staging. Traditionally, biopsy has frequently been accomplished using image-guided techniques, or in the case of paratracheal masses and lymphadenopathy, via mediastinoscopy. While these techniques are still often utilized and necessary, less invasive endoscopy techniques are evolving.

Endobronchial ultrasound (EBUS)

Early descriptions of EBUS demonstrated promise with this minimally invasive technology (19), but as the technology and equipment have evolved in the last decade, the diagnostic potential has increased dramatically. Perhaps the central advantage of EBUS is that is allows for transbronchial fine needle aspiration of centrally located mediastinal lymph nodes and other masses. As operators have gained experience, the diagnostic accuracy has increased. In patients with mediastinal adenopathy, meta-analysis demonstrates sensitivity and specificity approaching 92% and 100%, respectively (20). When EBUS is used for staging in patients with NSCLC, accuracy remains high, but the negative predictive value is only 89% (21). Therefore, a negative pathologic finding necessitates another biopsy method, most often, mediastinoscopy. When combined with rapid on-site cytopathologic evaluation (ROSE), the diagnostic accuracy is increased (22,23), although ROSE is not available at all centers. EBUS can successfully evaluate lymph node stations 2, 3, 4, 7, 10, and 11 (24,25).

The technical aspects of EBUS are challenging, but the learning curve can be overcome, and EBUS affords the thoracic surgeon a useful and less invasive diagnostic tool when compared to traditional mediastinoscopy. Using the preoperative cross sectional imaging as a reference, the EBUS scope is advanced to the area in question and the lymph node to be biopsied is identified using the displayed ultrasound image. Usually the lymph node(s) is clearly identified on the ultrasound display, but if the image is not clear, color Doppler may be helpful to rule out a vascular structure prior to biopsy. After identification of the target lesion, a 21-guage fine needle aspiration system is advanced through the working port of the EBUS scope. After advancing the needle into the lymph node, the internal wire is withdrawn, suction is applied, and several quick passes are made with the needle through the lymph node. The aspirated material can either be immediately analyzed (ROSE) or examined as a permanent specimen. It is common that EBUS operators examine only radiologically suspicious lymph nodes identified on CT or PET. However, mediastinal lymph node staging requires thorough evaluation of all visible N2 lymph nodes in order to identify possible occult N2 and/or N3 disease. EBUS is an enormous advance in minimally invasive mediastinal staging. However, inadequate sampling and a high false negative rate warrants proceeding to mediastinoscopy in patients with a suspicious or high-risk mediastinum, but a negative EBUS.

Electromagnetic navigational bronchoscopy (ENB)

Bronchoscopy has played a role in the diagnosis of NSCLC and other tumors for many years, however diagnostic methods have been limited to lesions within the observable airways, bronchial brushings and washings, and fluoroscopy guided lung biopsy. EBUS may be a reasonable alternative for proximal tumors, but generally is not helpful for peripheral tumors. The development of ENB has allowed for diagnosis of lesions within the lung periphery that cannot be visualized with standard flexible bronchoscopy, and affords diagnostic accuracy that exceeds that of bronchial washing. Computed tomography (CT) guided fine needle aspiration or core needle biopsy has been the predominant method of biopsy for peripheral lung masses and nodules, with a sensitivity of approximately 90% (26,27). Unfortunately, this high sensitivity is also associated with high rate of pneumothorax (~25%), requiring tube thoracostomy in up to 5% (28,29). The risk is particularly

high for patients with emphysema (29). ENB allows for biopsy of peripheral lung lesions with a diagnostic yield approaching 70% (30-32). The diagnostic power is improved when a bronchus sign is present (an observed bronchus leading directly to the lesion) (33) and with the use of ROSE (32). Complications are rare and the rate of pneumothorax is approximately 1–2% (30-32).

ENB, while effective and safe for diagnosis of peripheral lung masses, can be time consuming, as there are multiple phases to the procedure. The planning phase involves uploading a CT scan using the software from the ENB platform and virtually navigating to the lesion to identify the best pathway. With the patient positioned on a location board, the system is calibrated, the operator navigates to the lesion, and samples the lesion using one or more of a variety of instrument options. ENB can also be used to guide pulmonary resection through placement of fiducial markers or injection of blue dye.

Endobronchial valves

Lung volume reduction

The National Emphysema Treatment Trial (NETT) demonstrated the efficacy of lung volume reduction surgery (LVRS) in appropriately selected patients (34). However, in the NETT, mortality was 5.5% and morbidity was high with 59% of patients experiencing a significant complication (35). In an effort to provide similar benefit seen in the NETT with decreased risk and cost, several endobronchial valve systems were developed and designed to function as one-way valves that allow air to escape, but not enter, the airway in which they are placed (36). Early multicenter results demonstrated subjective improvement in symptoms and quality of life with no procedure-related mortality and a low incidence of adverse events (37). Despite this, a randomized, multicenter, double-blinded trial failed to demonstrate a clinically meaningful impact, even though there was a statistically significant improvement for patients who underwent endobronchial valve placement (38). While there is encouragement in the early experience with endobronchial valves as an alternative to LVRS, more studies are needed to gain a better understanding of appropriate patient selection and long-term efficacy.

Management of air leak

Air leaks are a frequently encountered phenomenon for the

practicing thoracic surgeon and be a result of spontaneous pneumothorax, or iatrogenic, related to thoracic surgical procedures, pulmonary resection, or lung biopsy. Prolonged air leaks, lasting for more than 5–7 days after secondary spontaneous pneumothorax are not uncommon, particularly in patients with emphysema, 20% of who develop a prolonged leak (39,40). Pulmonary resection is also associated with a high incidence of air leak, with rates of 10% after lobectomy (41) and 45% after LVRS (42). Treatment of prolonged air leak remains a difficult challenge. Perhaps the most common approach is to delay removal of chest tubes until resolution of the air leak. This practice is appropriate for most air leaks, although it is often associated with patient discomfort and may potentially be a source of infection or empyema. Other techniques, such as blood patch, pleurodesis, and operative repair have been describe with varying degrees of success.

Due to the morbidity associated with prolonged air leaks and the lack of effective therapies, bronchoscopic solutions have been attempted. The Watanabe spigot was developed as an early bronchoscopic intervention and was met with some success, with stoppage of 40% of air leaks and reduction in another 38% (43). We and others have had success using endobronchial valves for this purpose (44). The technique involves selective airway occlusion with a balloon catheter while observing the air leak within the chest tube over a period of approximately 1–2 min. It is then possible to deploy and position the endobronchial valve in the affected airway or airways. This technique has been reported with high success rates, including complete or partial resolution in 48% and 45% of patients, respectively, for an overall effectiveness of 93% (45).

Conclusions

Airway endoscopy is an extremely useful tool in the diagnosis and treatment of a variety of thoracic pathologic conditions. Flexible and rigid bronchoscopes are widely available for use, although the rigid bronchoscope affords significantly more interventional opportunities. While mastery of rigid bronchoscopic techniques is challenging, it is a critical skill for practicing thoracic surgeons. Recently, bronchoscopy has continued to evolve into minimally invasive diagnostic and treatment options, such as ENB and endobronchial valves. Airway endoscopy promises to remain at the forefront of thoracic interventions as we continue onto the future.

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Techniques of endoscopic airway tumor treatment

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Abstract: Interventional bronchoscopy has a predominant role in the management of both early and advanced-stage airway tumors. Given the very poor prognosis of lung cancer, there is a need for new tools to improve early detection and bronchoscopic treatment of endo-bronchial precancerous lesions. In more advanced stages, interventional bronchoscopy plays an important role, as nearly a third of lung cancers lead to proximal airway obstruction. This will cause great discomfort or even life-threatening symptoms related to local extension, such as dyspnea, post-obstructive pneumonia, and hemoptysis. Surgery for very locally advanced disease is only effective for a limited number of patients and the effects of conventional antitumor therapies, like radiation therapy or chemotherapy, are inconstant and are too delayed in a palliative context. In this review, we aim to provide pulmonologists with an exhaustive technical overview of (I) the bronchoscopic management of benign endobronchial lesions; (II) the bronchoscopic management of malignant tumors, including the curative treatment of localized lesions and palliative management of malignant proximal airway stenosis; and (III) descriptions of the emerging endoscopic techniques used to treat peripheral lung tumors.

Keywords: Interventional bronchoscopy; central airway obstruction; lung cancer; laser; brachytherapy; airway stent

Introduction

Interventional bronchoscopy mainly concerns malignant tumors (bronchogenic carcinoma in 70% of cases, metastatic malignancies in 25% of cases in our institution) but also benign tumors (5% of cases).

Lung cancer has the particularity of being tardily symptomatic, making early diagnosis a far too rare event. No screening program has yet been validated in most countries, and improvements to the early detection of metaplastic changes in selected populations are very challenging. For the same reasons, lung cancer is usually diagnosed at an advanced stage, and frequently from symptoms related to local progression of the disease, when conventional treatments offer inconstant and delayed benefits. In contrast, new bronchoscopic approaches that visualize peripheral nodules using radial-probe endobronchial ultrasonography (RP-EBUS) and electromagnetic navigation (EMN) are paving the way towards new bronchoscopic management of early-stage peripheral lung cancers.

Herein, we present an exhaustive description of the overriding role of the interventional pulmonologist in the management of pre-invasive, localized, and locally advanced lung cancer. We will detail: (I) the place of bronchoscopy in the curative treatment of benign pediculate endoluminal tumors; (II) the specific indications, results, and limitations of the bronchoscopic tools to detect and offer a curative treatment for localized neoplastic lesions, and the management of malignant central-airway obstruction; and

(III) discuss the emerging endoscopic approaches used for curative treatment of peripheral lung cancer.

Curative treatment of endobronchial benign tumors

Bronchoscopic treatment of benign tumors should be restricted to strictly endoluminal polypoid tumors (<15 mm^2 base), without any signs of submucosal-layer infiltration. Involvement of the airway wall must be precisely assessed by a CT-scan or ideally by more precise tools. RP-EBUS should be considered before treating such benign tumors as it can detect invasion of the cartilage layer with a sensitivity of 86% and a specificity of 100% (1). In 1995, Shah *et al.* reported "very good" and "good" results in 62% and 38% of patients, respectively, after bronchoscopic management of 185 benign airway tumors. The main technique used in these cases was laser resection (2). Bertoletti *et al.* then described the usefulness and the very good results from using cryotherapy on the implantation base of 18 strictly endoluminal and typical carcinoid tumors (3). This approach can be used for other benign tumors (4,5).

Bronchoscopic techniques for the curative management of early stage non-small-cell lung cancer (NSCLC)

Techniques for detection and local staging

Given the very poor prognosis of lung cancer, efforts have been made to improve the early detection of precancerous lesions. Indeed, 37% of severe dysplasias and 87% of *in situ* carcinomas evolve into invasive cancer, although less commonly in the presence of slight or moderate dysplasia (3.5%) (6). Furthermore, close surveillance is indicated for every patient that survives an initial lung cancer, as the risk of developing a second carcinoma ranges between 2% and 14% per patient per year (7,8). Different tools are available for the early detection and follow-up of these radio-occult tumors, for the screening of other endobronchial lesions before thoracic surgery, and to guide bronchoscopic curative treatments. Local staging includes evaluation of the area and thickness of the lesion.

Autofluorescence can differentiate dysplasia and cancer lesions from normal tissues based on their respective concentrations of endogenous fluorophores. The decrease in the extracellular matrix and the increased concentration of porphyrin that characterizes dysplastic tissue will thus correspond, in the autofluorescence bronchoscopy or autofluorescence imaging, to defects in fluorescence or to magenta-colored areas, respectively (9). Nevertheless, if sensitivity is good (0.9), the major pitfall of autofluorescence is its low specificity (0.56) (10); resulting in an increased number of useless biopsies (false positives). However, the results strongly depend on the predetermined definition of "positive biopsy" (i.e., 71.1% specificity for severe dysplasia and carcinoma *in situ*) (11).

Narrow-band imaging enables analyses of submucosal microcapillary structures, with different pathologic patterns described in dysplastic or cancerous tissues (grid dotted, tortuous, abrupt-ending blood vessels) (12,13). The advantage of this technique compared to autofluorescence imaging resides in its improved specificity (90% *vs.* 52%) (14).

Probe-based confocal laser endomicroscopy may further improve the diagnostic accuracy of bronchoscopy when screening pre-invasive metaplasia. The first data suggest good sensitivity (96%) and specificity (87%), which could be increased by topical instillation of exogenous fluorophores, such as acriflavine (15).

RP-EBUS can be used to evaluate the depth of invasion within the cartilaginous layer with good specificity (77%) and sensitivity (88%) (16-18). In addition, any adjacent suspected lymph nodes can be sampled by needle aspiration using linear EBUS, which is an established technique used in lung-cancer staging.

Optical coherence tomography may also help to assess parietal extension of radio-occult lesions (19).

Techniques used for the curative treatment of pre-invasive or minimally invasive lesions

Surgical resection remains the gold standard in early-stage NSCLC (20). However, bronchoscopy offers different options for the treatment of carcinoma *in situ* or slightly invasive endo-bronchial lesions, with good results, low morbidity, and low cost. Indeed, many patients with poor lung function or other comorbidities can then avoid surgery.

Smokers can develop multiple pre-neoplastic lesions and synchronous or metachronous squamous carcinomas within the entire upper aerodigestive tract, based on the principle of "field cancerization" (21). The main advantage of endoscopic treatment is thus the preservation of lung parenchyma and lower morbidity mortality, whereas the major risks are potential underestimation of the extension of the tumor and a lack of care regarding lymph-node metastases (22). The best candidates for bronchoscopic treatments are patients with lesions measuring <10 mm

Table 1 Results and limitations of the main available bronchoscopic techniques used for curative treatment of endobronchial lesions

Methods	Principle	Indications	Results/advantages	Limitations
Photodynamic therapy	Local activation of a photosensitizing agent using a specific wave-length (630 nm) Phototoxic reaction	Maximum 6–7 mm depth lesions; extensive/ multiple lesions	Tumor response 70%; 5-year survival 70% for TIS or stage I; widely studied	Cost; sunburn
Brachytherapy	Radioactive isotopes (Iridium 192) delivered through a graduated radio-opaque catheter	Radio-occult lesions, <3 cm infiltration; inoperable patients; contralateral recidive after pneumonectomy; incomplete resection surgery	2 years-survival rate 92%; 2 years-local control rate 86%; depth of action; synergistic association with external radiation therapy; widely studied	Risk of fatal hemoptysis; radiation bronchitis/ necrosis/fistula/ stenosis
Cryotherapy	Cold cytotoxic effect (dehydration, crystallisation)	Endobronchial superficial lesions; no cartilaginous invasion; <3 mm depth	91% histological remission; no fire risk; cheap; no risk of stenosis or perforation	Limited thickness of action (3 mm)
Thermocaogulation	Thermic destruction of the tissue by a high-frequency electric current	From severe dysplasia to micro invasive carcinoma	80% complete response rate; cheap; quick; available in many centers	Risk of bleeding; stenosis; perforation; poor littérature

without extra-cartilaginous invasion (23). Once the histological nature and extension are assessed, different tools are available, with each having preferential indications, specific mechanisms of actions, and risks. These data are summarized in *Table 1*.

Brachytherapy

Brachytherapy is a highly localized radiation therapy that preserves healthy tissue. Radioactive isotopes (iridium-192) are delivered to the tumor through a graduated radio-opaque catheter (24). Catheters are placed through a large bronchoscope, their position controlled by fluoroscopy. The target volume is assessed based on endoscopic findings (usually helped by autofluorescence imaging) and 3D-treatment planning is then calculated from radiographic data after placement of the catheter(s). *Figure 1* shows each step during treatment of endoluminal T1 squamous-cell carcinoma in a patient recused for surgery.

Brachytherapy should be considered as a curative treatment in radio-occult lesions, endobronchial infiltration for patients with respiratory insufficiency, controlateral recurrence after pneumonectomy, or as a complementary technique for incomplete resection surgery (25-29).

The largest cohort to date included 226 patients that had undergone brachytherapy (97% squamous cell carcinomas and had been treated with high-dose rate

(HDR) brachytherapy because they had contraindications for surgery or external-beam radiation therapy. Repartition was 26% Tis, 67% T1, and 0.04% T2. A complete bronchoscopic response at 3 months was observed in 93.6% of patients. The 2- and 5-year survival rates were 57% and 29%, respectively. Fatal hemoptysis occurred in 5% of cases, bronchitis in 19.5%, with 3.5% necrosis. These complications were shown to be associated with the use of two catheters and having a distal localization (27).

A combination of external-beam radiation therapy and HDR brachytherapy has also been proposed to treat endobronchial carcinomas as an alternative to surgery, and has achieved high response and survival rates. In this study, Kawamura *et al.* included 16 lesions, of which 10 were treated with HDR brachytherapy (20 Gy) combined with external-beam radiation therapy (45 Gy), and 6 lesions were treated with HDR brachytherapy alone (25 Gy). The 2-year survival and local-control rates were 92.3% and 86.2%, respectively. Local recurrences were observed in only two lesions (30).

This method is expansive and remains suited for deeper lesions compared to the techniques described below. Acute side effects of this procedure include pneumothorax, bronchospasm, hemoptysis, pneumonia, and cardiac arrhythmia. Radiation bronchitis and stenosis may occur as early and delayed complications. Interventional bronchoscopy is sometimes required in cases of
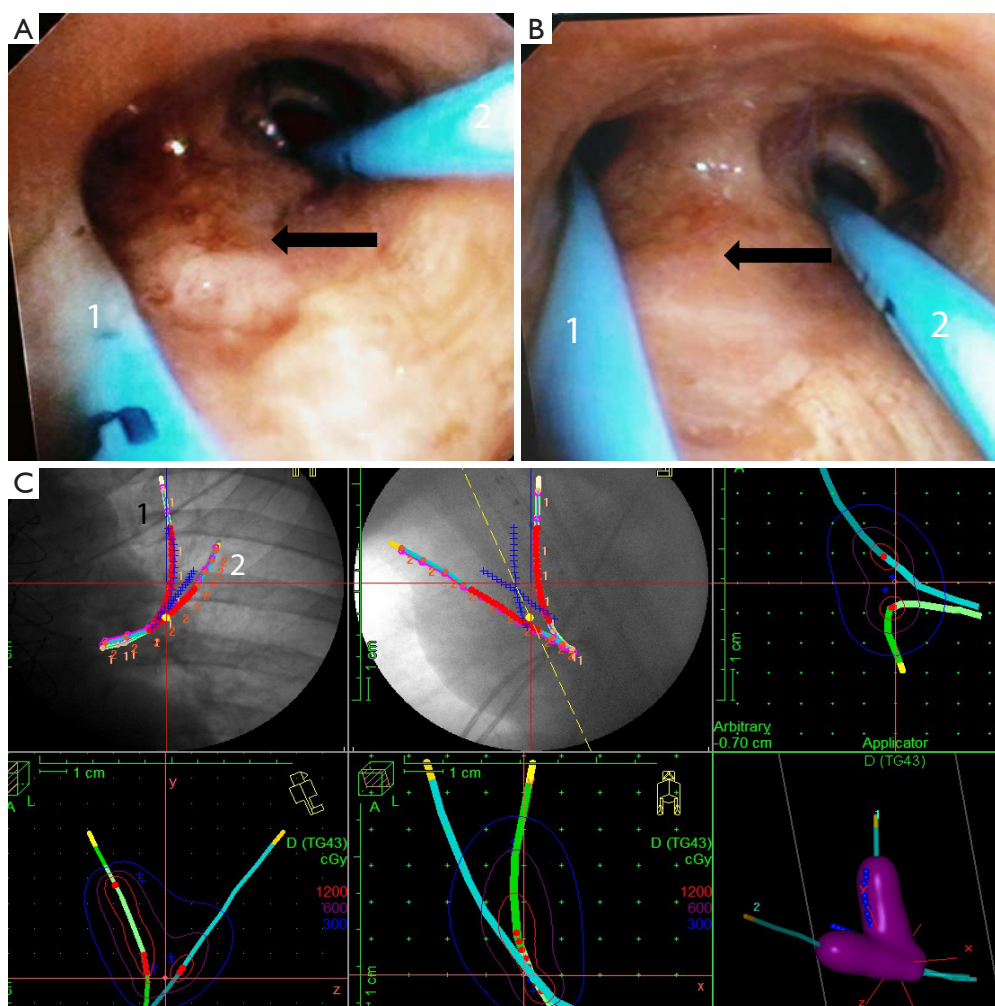
Figure 1 Example of brachytherapy for an endobronchial infiltration of the upper left lobe. Bronchoscopic view of the two catheters (1= apical of the culminal bronchus; 2= anterior segment of the culminal bronchus); showing local dramatic improvement: before (A) and after (B) the three first fractions (6 Gy); (C) planning of dose distribution from radiographic images.

symptomatic stenosis (balloon dilatation, laser resection, or airway stenting) (31).

It is sometimes difficult to differentiate complications linked to tumor progression from those related to brachytherapy (32). The most serious potential side-effects from brachytherapy are fatal hemoptysis and fistula formation. Death from massive hemoptysis has been reported in up to 7% of patients (n=342), but occurred mainly within palliative settings, and this complication seems rarer in the context of minimally invasive lesions (33).

Photodynamic therapy (PDT)

The principle of bronchoscopic PDT resides in the local activation of a photosensitizing agent (most commonly a hematoporphyrin derivative) using a light source with a specific wave-length (630 nm) that induces a phototoxic reaction and cell death (24,31-33). Bronchoscopic PDT for lung cancer is a two-step procedure: photosensitization and illumination. After intravenous injection of a photosensitizer (photosensitization) and a 72-h latent period, bronchoscopic illumination is carried out. Other photosensitizers have been tried (ALA or Npe6) (34). The depth of action is 6–7 mm and the surface diffusion of light allows, in theory, treatment of slightly more extensive lesions than other techniques. Moreover, this technique can still be used when the tumor area cannot be precisely identified by narrow-band imaging or autofluorescence imaging. Depending on the number

and extent of the treated lesions, PDT can be performed under local or general anesthesia, sometimes secured by rigid bronchoscopy.

Many studies have reported on the efficiency of PDT in treating central-airway obstructions (reported in the next chapter), and early stage and minimally invasive endobronchial tumors. Corti *et al.* reported a 5-year survival rate of 60% amongst 40 patients with CIS or minimally invasive diseases (35). Moghissi *et al.* collected data from PDT used for early-stage NSCLC in 13 studies (n=523 patients). Tumor response to treatment was observed in >70%. The 5-year survival amongst patients that experienced complete remission after treatment of TIS or stage-I diseases was 70%. After exclusion of deaths not related to cancer, the 5-year survival was 90% for TIS (36).

PDT is generally well tolerated. Skin photosensitivity is the most common side effect (8–28% of cases), which is usually grade I, justifying avoiding sunlight for the 6 weeks after treatment (31,36). Dyspnea may be caused by airway obstruction from necrotic debris, local airway edema, or delayed strictures, but these complications are less common in the context of early-stage disease than in a palliative situation. Fatal hemorrhage and fistulas were also very rarely reported in this indication.

Cryotherapy

Cryotherapy is the application of very low temperatures (89.5 ℃) using cryogenic liquid gas (N_2O, N_2, CO_2) to destroy tumor tissues (24,34,35,37). The mechanisms of action are associated with immediate (dehydration and cellular crystallization) (31,37-40) and delayed (apoptosis, ischemia caused by microthrombi formation) effects (31,39,41). At least three cycles of freezing and thawing are applied to the treatment area through the tip of a flexible or rigid cryoprobe. The whole surface should be treated with 5-mm spacing between each new application of the probe (31).

Deygas *et al.* reported 91% histological remission rate at one month in a multicenter study (n=35). Local recurrence was observed in 28% of cases within 4 years (41). Noppen *et al.* also reported favorable outcomes in four patients (42). Cryotherapy possesses many advantages: it is very cheap and safe (41) because the risk of airway ignition, perforation, or delayed stenosis is non-existent, and it has a good hemostatic effect (35,43). Its major pitfalls are the narrowness of the treatment area and the depth of its cytotoxic action, which is limited to 3 mm (44).

Thermocoagulation

Electrocoagulation (or electro-cautery) is a coagulation technique. A high-frequency electric current is delivered through the tumor tissue, which generates heat and destroys it (24). The probe is placed in close contact to the target tissue area and the energy setting can then be changed depending on the expected effect. A small study that included 15 <1 cm endobronchial lesions in 13 patients showed an 80% complete-response rate and no recurrences after 22 months of follow-up (45). It can be applied through flexible or rigid probes, under local or general anesthesia (46). It is inexpensive and available in all surgical wards, but some complications can occur, such as bleeding.

In conclusion, all of these methods show promising outcomes. Brachytherapy seems to be most suited to deeper lesions and PDT to extensive and/or multiples lesions, especially when the tumor area cannot be precisely identified. Nevertheless, more prospective controlled studies need to be conducted to help clinicians choose the right technique for each specific case. Associations of these different tools together with stereotactic radiotherapy or systemic treatment should also be evaluated.

Available techniques for the management of central-airway obstruction

Between 20% and 30% of lung cancers cause central-airway obstruction (CAO), resulting in dramatic alterations to quality of life and a poor prognosis. CAO can be linked to purely endoluminal tumors, extrinsic compression, or a combination of both. Multiple bronchoscopic tools are available to relieve these obstructions depending on the mechanism of the stenosis, and can be split into four main categories: (I) mechanical debulking, usually used with other techniques for intraluminal lesions; (II) thermal techniques, which have an immediate effect on severe and/or very symptomatic intraluminal stenoses; (III) thermal techniques that have a delayed effect on non-threatening intraluminal stenoses; and (IV) airway stenting for extrinsic compressions.

All these methods can be used alone or in combination (47). The precise place of each technique and the eventual superiority of one over another remains undefined, as no large clinical trials or comparative studies have been conducted. The choice of technique thus depends on the choice of the operator and the techniques available. The principles, results,

Table 2 Principles, results, and pitfalls of the techniques available for the bronchoscopic management of malignant central-airway obstructions

Methods	Principle	Indication	Advantages	Limitations
Mechanical debulking	Resection with the beveled end of rigid tubes and rigid forceps	Proximal, slightly hemorrhagic intraluminal lesions	Rapidity; cost	20% severe complications (bleeding, perforation)
Thermal techniques with immediate effect				
Laser	Short pulsations in the bronchial axis	Critical intraluminal obstructions	Rapid, immediate, and prolonged effect	Cost; perforation and fistula risks
Electrocoagulation + argon plasma coagulation	High-frequency electric current +/− argon as a carrier gas (APC)	Intraluminal proximal obstructions	Cost; low risk of perforation; APC: extended and hemorrhagic lesions	Risk of cicatricial stenosis if circumferential treatment; cost for APC
Thermal techniques with delayed effect				
Cryotherapy	Expansion of a cryogenic gas; cycles of rapid freezing and slow thawing	Non-critical endoluminal obstructions (except cryoextraction and spray cryotherapy)	Low cost; easy procedure; no perforation; prolonged efficacy	Delayed effect (except cryoextraction and spray cryotherapy); retention of tumor material
Photodynamic therapy	Activation of a photosensitizer by light; phototoxic reaction, cell death	Intraluminal or mixed nonthreatening obstructions	Good symptom control (hemoptysis); prolonged efficacy	Delayed effect; retention of tumor material; cleaning bronchoscopy; phototoxicity; cost
Stents				
Silicone stent	Inserted via rigid tube; adjustment with a forceps	Extrinsic or mixed obstructions	Good tolerance; few local granulomatous and ischemic reactions; easily removable	Systematic general anesthesia and rigid bronchoscopy; altered ciliary clearance; risk of migration (rare, except in case of purely extrinsic compression)
Metallic stent	Under radiographic or bronchoscopic control; flexible or rigid bronchoscopy; self-expandable	Second intention, except in cases of highly necrotic lesions, fistula or high distortion	Easy placement; preserved clearance	Risk of granuloma, perforation; hardly removable

APC, argon plasma coagulation.

and pitfalls of each technique are summarized in *Table 2*. Two examples of scanographic and bronchoscopic results after mechanical debulking, thermo-coagulation, and airway stenting are represented in *Figures 2* and *3*.

Indications

Interventional bronchoscopy is an invasive treatment and should only be used in cases of symptomatic obstruction and in the presence of a viable downstream bronchial tree and parenchyma. A CT-scan and flexible bronchoscopy are thus the two essential tools to both check the viability of the distal airways and the precise mechanism of the stenosis.

Significant improvement to quality of life and symptoms can be expected for obstruction involving large airways (trachea, main bronchi, *bronchus intermedius*). Interventional bronchoscopy for a more distal tumor must only be proposed to control hemoptysis or draining-retentional pneumonia (48). Beyond this technical aspect, selection of the patient that will benefit most from this treatment is crucial, but is sometimes difficult. We reported some strong predictive factors for sustained efficiency in a retrospective analysis of 204 patients (49). A study is currently recruiting patients to prospectively validate these results on survival and, above all, will try to identify the predictive factors for improvement to quality of life. We hope this study will help
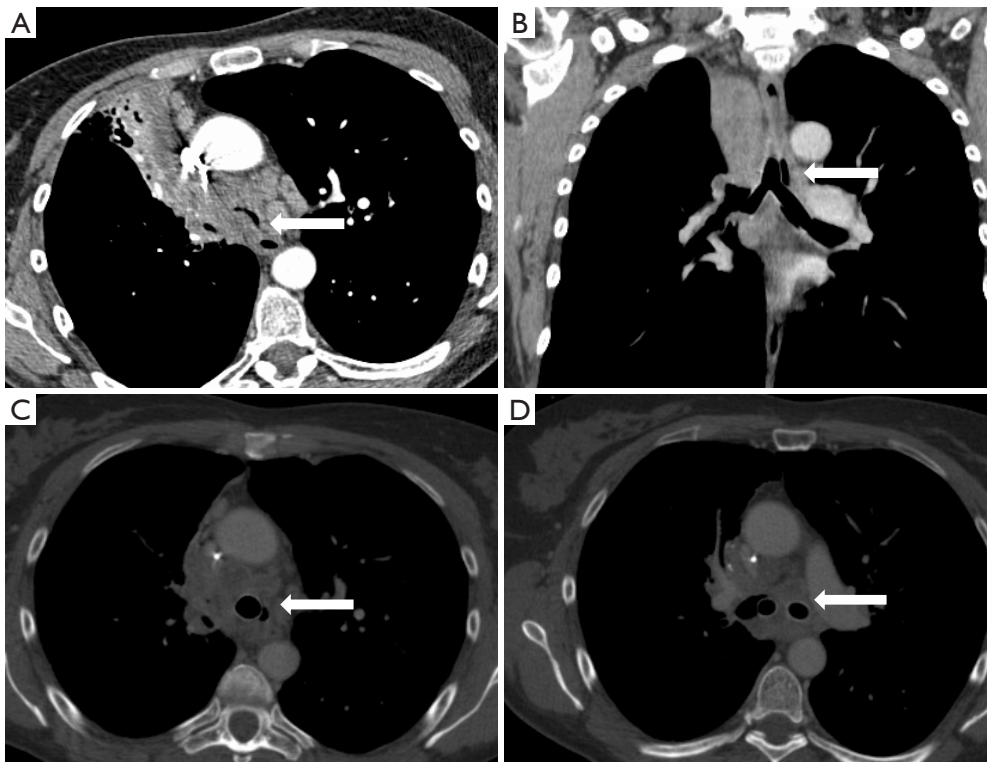
Figure 2 Example of a scanographic result after laser treatment, mechanical debulking, and airway stenting (a Dumon Y stent®) of a life-threatening malignant central-airway obstruction involving the carina (A); (B) frontal view after airway stenting; (C,D) scanographic sagittal views after airway stenting.
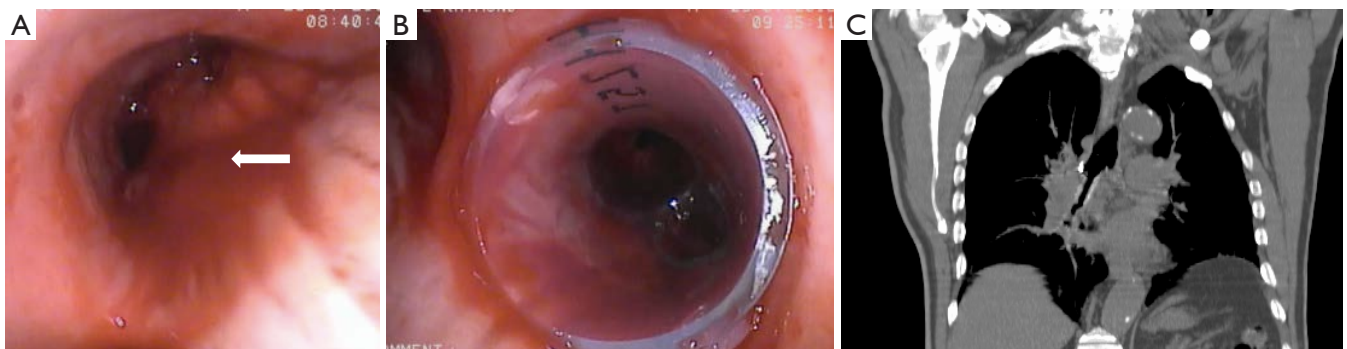

Figure 3 Example of a bronchoscopic result after stenting of the primary main carina for a malignant stenosis of the right main bronchi. (A) Extrinsic compression of the right main bronchus; (B) result after airway stenting (a Dumon Oki stent®); (C) CT-scan after stenting.

clinicians to select the best candidates and to avoid giving an invasive treatment to others.

Modalities

Rigid bronchoscopy offers advantages in terms of airway control, the ability to easily remove large volumes of tumor, and to deploy silicone stents: this method should, in our opinion, always be favored. Treatment through a flexible bronchoscope and local anesthesia, or under slight sedation and a laryngeal mask, may be considered for small, nonthreatening, and slightly hemorrhagic tumors, when the expected time of procedure is short. When rigid bronchoscopy is chosen, different types of ventilation can

be proposed: i.e., manual with a bag-valve mask, or jet ventilation (high frequency, high pressure, low volume) (48).

Techniques with an immediate effect

In cases of threatening and/or very symptomatic intra-luminal CAO, an immediate, rapid, and safe technique must be chosen. Mechanical debulking, electrocoagulation, and laser are the most widely used techniques in this context.

Mechanical debulking

Rapid debulking of intraluminal tumors can be obtained with either the beveled end of different-caliber rigid tubes or with a large clamp. However, except in cases of proximal and low-risk hemorrhage tumors, this approach usually needs to be combined with one of the thermal techniques described below, as it is associated with high rates of complications when used alone (i.e., ~20% of cases), such as pneumothorax, hemoptysis, and pneumonia (50). For example, an ideal sequence is, combined with a laser: (I) hemostasis by tumor coagulation at 30 W; (II) mechanical debulking; (III) destruction of the residual tumor tissue at 50 W; and (IV) final treatment at 20–30 W on the implantation base for a prolonged cytotoxic effect (51,52). A minimum of 15–20 supervised procedures are required to reach autonomy with a rigid bronchoscopy (53).

Thermocoagulation

This method offers rapid relief from malignant proximal intrinsic compressions. A high-frequency electric current is delivered to the endoluminal tumor obstruction through a flexible or rigid probe of varying diameter and form, such as a coagulation electrode, loop, or hot-biopsy forceps (24,31,54-56). New-generation generators can be set to different modes (55). The "soft-coagulation" mode prevents airway fire, maintaining relatively low temperatures (<200 ℃). "Forced coagulation" is more risky but allows rapid debulking by tissue carbonization. Symptomatic palliation is obtained in 96% of cases and concords with functional improvement (55,56). Major complications are rare, and the particular risks of perforation and ignition are non-existent in soft-coagulation mode (55,57-59). Circumferential thermocoagulation of an airway may result in scarring stenosis (53,60,61). Thermocoagulation must therefore been considered as the first-line treatment for intra-luminal tumors as it is highly efficient, only moderately expensive, and is very safe.

Argon-plasma coagulation

The limitations of electrocoagulation include restricted access to the most apical segments and loss of efficacy when there is active bleeding. These two drawbacks are overcome by using argon as a carrier gas (non-contact method), but this technique requires an additional probe and a generator (24,31,57,62). Argon (and thus electric current) is transported to the affected vessels through the bloodstream, allowing good control of the hemorrhage (100%) (62,63), even if the origin of bleeding cannot be precisely identified (24,53,55,64,65). This makes this tool particularly suited for extensive and hemorrhagic lesions.

Laser

This method is the fastest and thus the most suitable technique for life-threatening intraluminal critical obstruction. It uses different gases (CO_2, potassium titanyl phosphate, Nd:YAG, and a diode laser) to rapidly photocoagulate and destroy tumors (24,53). An immediate bronchoscopic result (92% of cases) is usually obtained, and the more proximal the tumor, the better the result (66). This re-permeabilization results in constant and significant improvement in symptoms, quality of life, arterial blood gas, and spirometric analyses (67,68). The results are globally equivalent to those reported with thermo-coagulation (55,69) but laser treatment may shorten the procedure, even though these two techniques have not been prospectively compared. The risk of airway fire only appears beyond the 0.4 FiO_2 level and can thus be prevented by good communication between the anesthesiologist and pulmonologist (68,70). Hemorrhages are not rare, but can be usually efficiently controlled by cold serum, adrenaline, local instillation of terlipressin, compression with the tube, or short electrical pulses of <30 W. Severe hemoptysis only occurs in 1% of cases (52,67,70).

The major potential lethal complication, related to a high depth of action, is perforation of the tracheobronchial wall to cause a vascular fistula, gas embolism, and/or mediastinitis (70,71). This event can be avoided by respecting a tangential axis of treatment and a non-contact treatment (1 cm). Although the mortality rate is low [reported as <1% (31,68,69,71)], one pitfall of this technique is its high cost, which may be prohibitive in some centers due to the price of the generator and because of the single-use probes, with costs much higher than for electro-coagulation (54,64,69).

Cryotherapy with an immediate effect

Cryotherapy can be delivered through a flexible or rigid

probe (40,72,73). This procedure is known to have delayed effects (74) and, thus, is not suitable for cases of threatening stenosis. Nevertheless, two modalities can still be considered in this context.

(I) Spray cryotherapy is a technique that enables low-pressure liquid nitrogen (–196 ℃) to be administered, and produces immediate effects. The treatment area is extensive and the hemostatic effect is excellent. This technique, like APC, should therefore be preferentially used in cases of hemorrhagic and extensive tumors, especially when the origin of bleeding is not easily identifiable. Nevertheless, this technique still requires validation and does not appear suitable for voluminous tumors, given that this intervention has a long duration (73).

(II) Cryoextraction uses a large probe (2.3 mm) and is another modality used to treat obstructive stenosis without risking perforation or residual stenosis; it has a low incidence of other complications (74).

Endoscopic dilatation

Balloons placed at the center of a malignant stenosis can allow mechanical debulking and dilatation by controlled inflating (3 to 6 atm. pressure) (75-77). However, the effect is transient, and this tool should only be considered as a complement with other techniques, especially as a first step before stent placement when there is an impassable obstruction.

Microdebrider

The microdebrider is mainly used by rhino-laryngologists and involves a rotating blade and suction. This combination shortens the procedure, as tumor debris are simultaneously aspirated, and allows for rapid and efficient debulking [98% of cases (78,79)].

Techniques with a delayed effect

When there is a nonthreatening and slightly symptomatic malignant stenosis, the indications for interventional bronchoscopy must be carefully discussed. Indeed, it depends on the other therapeutic options and the probability of these conventional therapies (radiation therapy, chemotherapy) succeeding (47). Histological subtype and its supposed chemosensitivity should especially be taken into account. In this context, cryotherapy is the most attractive tool due to its low cost, good efficiency, safety, and prolonged effects. Other techniques have been reported but, in our opinion, should not be considered as

first-line treatments in the context of palliative management of central-airway obstruction, like PDT or HDR brachytherapy.

Cryotherapy with a delayed effect

Except for particular cases of cryo-recanalization and spray cryotherapy (described previously), this technique is indicated in cases of non-obstructive and slightly symptomatic obstructions without acute respiratory distress, because of its delayed effects (24,55). This procedure offers good control of symptoms (especially hemoptysis), and improves quality-of-life scores, arterial blood gas, and spirometric parameters (35,37,80). A normal airway caliber can be recovered in 61–91% of cases (72,81,82), allowing for resolution of 57% and 76% of cases of total and lobar atelectasis, respectively (81). Its prolonged effect, strengthened by repetitive cryotherapy sessions, is related to an associated cytotoxic effect (74,83,84).

One major advantage of this tool is its safety. Mortality rate is low, reaching 1.2%, and is rarely directly linked to cryotherapy (80). The total complication rate is less than 10% (72,82). The risk of perforation is non-existent, as the cartilage is extremely cryo-resistant (31,72). This technique also has a low cost and a synergistic association with chemotherapy (85,86). The major caveat is its delayed effect, resulting in retention of tumoral material, which then needs bronchial aspiration performed at 1–2 days after (31,62,87).

PDT

The principle of bronchoscopic PDT resides in local activation of a photosensitizing agent (most commonly a hematoporphyrin derivative) using a light source with a specific wave-length (630 nm), which induces a phototoxic reaction and cell death (24,31,38,43,88). Like cryotherapy, PDT achieves good but delayed improvement, and is therefore contraindicated in cases of critical obstruction. This technique is particularly effective in controlling hemoptysis (99%) and dyspnea, and offers good bronchoscopic results and significant functional improvement (89-91). A synergistic effect with radiation therapy is probable (92).

However, this technique has major limitations. The drug is eliminated from most tissues within 72 hours, yet remains preferentially stored in the skin, liver, spleen (and in malignant cells), explaining the phototoxic reactions observed in 5–28% of patients. Avoidance to sunlight is recommended during the 6 weeks after treatment (52,91); however, this preventive measure appears to be
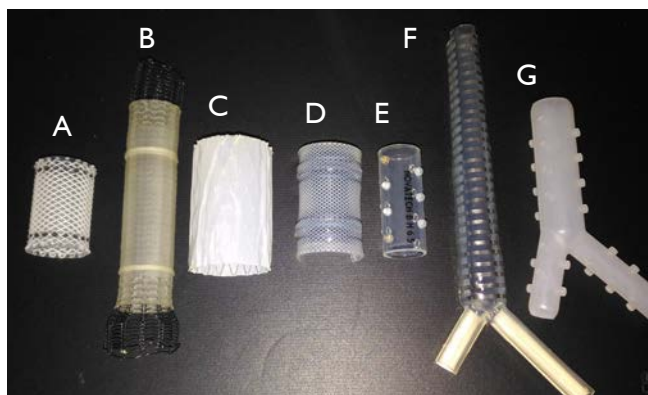
Figure 4 Examples of stents available: from left to right: (A) Polyflex®; (B) Covered Ultraflex®; (C) Silmet stent®; (D) Nova-Stent®; (E) Dumon stent®; (F) Dynamic Freitag® stent; (G) Hood stent®.

overly restrictive in a palliative context. In addition, a second bronchoscopy must be performed at 1–2 days later to remove necrotic tumor tissue and again at 5–7 days after to expose residual tissue to a second illumination (83,88,89,93,94). Furthermore, hemoptysis is a relatively frequent complication, reported in 18% of cases, of which 2.2% are fatal (89); the mortality rate is not negligible, reaching 9% during the first month (91).

Brachytherapy

Although brachytherapy, as described previously, still constitutes an interesting option for early-stage lung cancer, in our opinion, it should no longer be used for the palliative treatment of malignant obstructions. Symptomatic and functional improvements have been reported in older studies, with delayed efficiency, but the risk of severe complications has been major, reported at between 13 and 20% (33,95). Up to 7% of patients died after massive hemoptysis (33). Radiation bronchitis, which frequently exhibits a fatal evolution due to bronchial necrosis followed by abscess formation, affected 14–35% of patients (96,97). Nevertheless, experimental groups have reported good results and slightly better tolerance to this treatment. Interestingly, in a very large cohort (n=648) of patients divided into two groups that received a single fraction of 10 or 22.5 Gy in three fractions once a week, the clinical improvement was globally equivalent (98).

Local instillation of chemotherapy and gene therapy

Local intra-tumoral injection of chemotherapy has been attempted in the context of malignant central-airway obstruction. Celikoğlu *et al.* reported re-permeabilization in more than 80% of patients using different cytotoxic agents (5FU, mitomycin, methotrexate, bleomycin, mitoxantrone, cisplatin) (99-101). More recently, Mehta *et al.* also described good bronchoscopic results (defined as >50% reduction in airway stenosis from baseline) after intratumoral injection of cisplatin in 15/21 patients (102). Khan *et al.* obtained complete PET/CT remission of locally recurrent lung cancer after an EBUS-guided transbronchial needle-injection of cisplatin in a hilar lymph node (103).

Another promising approach is the bronchoscopic delivery of a recombinant adenovirus that carries wild-type *p53* into patients with NSCLC and that harbor the *p53* mutation. After monthly injections, 50% (6/12) of patients had airway obstruction improved by >25%, and 25% of patients showed a partial response (104). Combined with external radiation therapy (60 Gy), this strategy enabled 63% of cases to obtain local and complete-response rates (105).

Stents

Airway stenting is the only procedure available for the relief of extrinsic compression or trachea-esophageal fistulas (75,106,107). It has been widely used since Dumon designed a silicone stent, derived from Montgomery's T-shaped tracheal stent (which required a tracheotomy) (83,108). Self-expandable metallic stents dedicated to airways were concomitantly developed, after the transient use of endovascular stents (Gianturco), which were associated with a high risk of ischemic mucosal necrosis and thus of perforation (109). The ideal prosthesis should (I) be cost-effective; (II) be easy to place and remove; (III) not migrate; (IV) be rigid enough to resist airway compression, yet still flexible enough to mimic airway physiology; (V) not impair mucociliary clearance, and (VI) not induce granulomatous reactions (38,106,110). The most widely used stents are represented in *Figure 4*.

Experts suggest that a minimum of 5–10 procedures per year after 10–20 supervised procedures are required to maintain competence of airway stenting (24,55).

Silicone stents

In the context of malignant central-airway obstruction, we recommend silicone stents as the first-line treatment (109,111). Indeed, they are easy to place and remove, they are well tolerated, have a marked vault effect, and cause few granulomatous reactions (24,106,108). The Dumon (Tracheobronxane®, Novatech, La Ciotat, France) is the

most widely used stent (108). Alternatives are the Polyflex® stent (silicone expandable stent) (Boston Scientific, Natick, MA, USA), the Hood stent® (Hood Laboratories, Pembroke, MA, USA), and the Noppen stent (Reynders Medical Supply, Lennik, Belgium).

The Dynamic Freitag® (Rüsch, Kernen, Germany) stent has a flexible posterior wall that mimics the physiological behavior caused during coughing. This stent should theoretically be associated with a lower risk of granuloma because of the more homogeneous distribution of pressures (112,113). Silicone stents can be straight or bifurcated for stenoses that involve the carina or primary right carina (Oki stent) (106,114). The diameter and size are chosen based on scanographic and per-operative bronchoscopic data, which are then adjusted by cutting (37,75,108,115-117).

Symptoms and quality of life are immediately improved in the vast majority of cases (52,75). Symptomatic granuloma is rare (1%, n=306) (10,118). Migration risk mainly concerns short and purely extrinsic stenoses (24,38,118,119) and immediate subglottic stenoses are relatively rare in cases of obstructions of malignant origin [2–6% (119) of cases *vs.* 18% with benign stenoses (120)]. The overall complication rate has been reported as 9.4% (52).

The few limitations of silicone stents compared to self-expandable metallic stents are caused by a narrower internal diameter due to wall thickness, which results in altered mucociliary clearance (38,106): i.e., obstruction by secretions (14% of patients) (64,111), favored by bacterial colonization (121), which can be avoided by nebulizations and good hydration (24).

Self-expandable metallic and hybrid stents

Self-expandable metallic stents (Ultraflex®, Boston Scientific; Alveolus®, Charlotte, NC, USA, Aerstent® Leufen, Germany) can be placed under video-bronchoscopic or radioscopic guidance (122). Their advantages include a lower risk of migration, better preserved mucociliary clearance, and larger internal diameter (106). They also offer rapid and good control of symptoms, and improved quality-of-life scores and spirometric parameters (85,107,110). However, even if these stents can be placed under flexible bronchoscopy, we do not recommend this approach (except in cases of intubated patients with no access to rigid bronchoscopy), as the control of obstructive or hemorrhagic complications is more rapid under rigid bronchoscopy. Self-expandable coated stents are particularly suitable for trachea esophageal fistulas, for tight and highly distorted stenoses,

and for highly necrotic stenoses, as they avoid the need to bypass the stenosis with a rigid tube (which increases the risk of perforation) (107,109,118,123).

Major limitations include the risk of granulomatous reactions at the extremities (118); epithelialization with incorporation into the mucosa, thus rendering the stent difficult to remove after 3–6 weeks (116); a weaker vault effect (111); and an increased risk of perforation (109). The rate of significant complications is often high for these stents, reaching 16% in the first month and 13% afterwards (124). Early complications include pneumothorax, pneumonia, and migration (118). Hemoptysis and infections are seen in 10% of patients (125). At later stages, symptomatic granuloma formation is observed in 15% (118) to 27% of cases (126).

Drug-eluting stents

These may be an interesting way to prevent granuloma and malignant-tissue formation. This approach has mostly been evaluated in gastrointestinal endoscopy, with anticancer or antiproliferative (mTOR inhibitors) agents (127). A biodegradable cisplatin-eluting stent has been designed, dedicated to the central airways, but has not yet been tested in humans (128). The main pitfall of such a prosthesis may be an enhanced risk of a fistula caused by its antiproliferative action.

Bronchoscopic management of endobronchial metastases

Endobronchial metastasis of other solid tumors is relatively rare; it usually occurs tardily after the initial diagnosis (median 56 months) (129). A classification has been proposed to described their mechanisms: (I) type I is a directly endoluminal metastasis; (II) type II corresponds to bronchial invasion by a parenchymal lesion; (III) type III is the result of bronchial invasion by a mediastinal or hilar lymph node; and (IV) type IV are peripheral lesions extending along the proximal bronchus (129). Most frequently involved malignancies are breast, colon, and renal-cell carcinomas (130).

In a cohort of 24 patients undergoing bronchoscopic management of endobronchial metastasis from colorectal cancer, dramatic symptomatic and functional improvement was observed and median survival after the procedure was 14 months (131). Dalar *et al.* reported results from the bronchoscopic management of 20 procedures in nine patients suffering from endoluminal metastases of renal-cell carcinoma. The procedure was efficient in most cases with
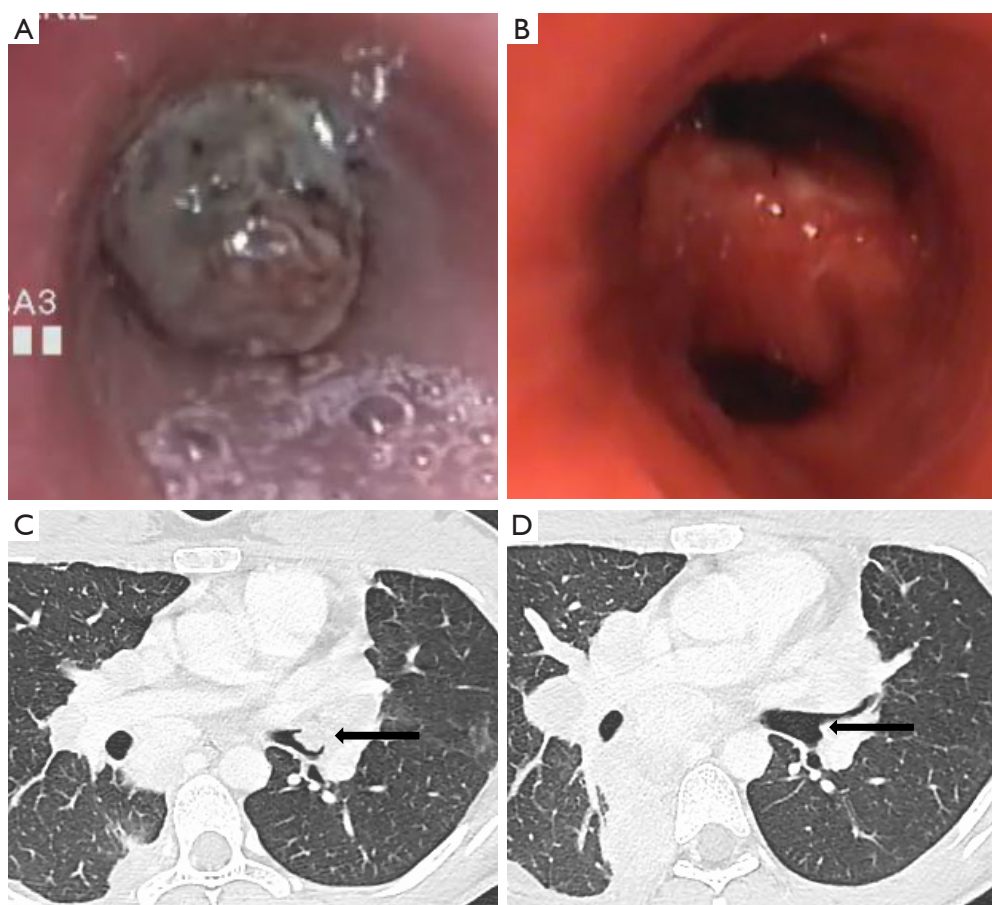
Figure 5 Bronchoscopic management of an airway metastasis (type I) from a fibrolamellar hepatocellular carcinoma. (A and C) Complete intraluminal obstruction of the left main bronchus (bronchoscopic and scanographic views); (B and D) results after laser and mechanical debulking.

median survival after the intervention of 8.7 months. The operator facing this histology has to be particularly prepared to face hemoptysis (60% of hemorrhagic procedures in this cohort) (12/20) (132). Bronchoscopic treatment of airway metastases from a melanoma is also usually efficient and does not show any technical particularities. Median survival after the procedure is 6 months (n=18) (133). *Figure 5* represents the results after bronchoscopic management of a type-I airway metastasis.

Emerging bronchoscopic techniques for the management of peripheral lung cancer

Although surgery remains the gold-standard treatment for early-stage lung cancer, alternative options have been developed to treat the most vulnerable and inoperable patients. Stereotactic body-radiation therapy has been evaluated the most and, thus, is the non-surgical treatment of choice, followed by percutaneous thermoablation. New bronchoscopic techniques that access distal nodules, mainly RP-EBUS, are paving the way towards new options to treat early-stage peripheral cancer (134).

Trans-bronchial CT-guided brachytherapy has been described in a few cases of peripheral lung cancer. Barium was injected through a catheter, placed under bronchoscopic control, to check its position with a CT-scan. Lateral and frontal X-rays allowed brachytherapy to be planned and iridium-92 was delivered using the HDR after-loading system. One of the two patients experienced a 75% decrease in tumor burden after a single dose of 15 Gy whereas the other patient did not respond after three fractions given at weekly intervals (total 24 Gy) (135). HDR brachytherapy

(three fractions of 5 Gy) was also delivered to a patient through a catheter that was placed using both EMN and RP-EBUS: this resulted in a durable partial response and a complete histological response in RP-EBUS-guided biopsy specimens at 12 months (136).

Because radiofrequency ablation has a high risk for pneumothorax, bronchoscopy-guided radiofrequency ablation has been reported as a safe alternative for selected patients. Amongst 23 peripheral lung cancers in 20 patients, 11 tumors showed significantly reduced tumor size and eight cases showed stability, resulting in a disease-control rate of 82.6% and a 5-year overall survival of 61.5%. Given these interesting results, we can anticipate a role for EMN and/or RP-EBUS to guide and thus improve the precision of this new strategy.

Other techniques should be evaluated for the treatment of peripheral early lung cancers, such as cryotherapy or PDT, which would be delivered through small cryoprobes/laser fibers after confirmation of the tumor location by EMN of RP-EBUS.

Finally, bronchoscopy has been evaluated as a tool for the placement of fiducial markers to guide real-time tumor-tracking radiation therapy for peripheral lung nodules (137). This option could also be improved by EMN of RP-EBUS.

In conclusion, the interventional pulmonologist holds an increasingly important place within each step of managing lung cancer. The early detection of pre-invasive endo-bronchial lesions is a current challenge, justifying the recent development of several tools with increased diagnostic accuracy and of mini-invasive techniques that have curative treatments.

In more advanced stages of lung cancer, interventional bronchoscopy offers many different possibilities to relieve central-airway obstruction when it is associated with a poor prognosis, and it greatly increases quality of life. The choice of technique ultimately depends on both the mechanism and the respiratory repercussions of the stenosis.

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Footnote

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Complications after tracheal resection and reconstruction: prevention and treatment

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Abstract: Tracheal resection and reconstruction (TRR) and laryngotracheal resection and reconstruction (LTRR) is commonly performed for post-intubation tracheal stenosis, tracheal tumor, idiopathic laryngotracheal stenosis (ILTS), and tracheoesophageal fistula (TEF). Ninety-five percent of patients have a good result from surgery. Complications occur in ~20% of patients, of which half are anastomotic complications. Complications include granulation tissue formation, restenosis of the trachea, anastomotic separation, TEF and tracheoinnominate fistula (TIF), wound infection, laryngeal edema, and glottic dysfunction. Risk factors for anastomotic complication include diabetes, reoperation, previous tracheal appliance, and long-segment tracheal resection. Bronchoscopy should be part of the diagnostic workup when a complication is suspected. Anastomotic separation—the most feared complication of tracheal surgery— may present subtly with stridor and wound infection, or with respiratory distress and extremis. Prompt management is required to prevent devastating consequences. The airway should be secured, bronchoscopy should be performed to address the degree of separation, and the anastomosis should be revised if needed, usually with the addition of t-tube or tracheostomy. Anastomotic complications that are managed aggressively typically yield good results. More than half of such patients will eventually have a satisfactory airway. However, an anastomotic complication is associated with a thirteen-fold increase in the risk of death following tracheal resection.

Keywords: Airway obstruction; laryngeal edema; tracheal stenosis; tracheoesophageal fistula (TEF); tracheostomy

Introduction

Tracheal resection and reconstruction (TRR) and laryngotracheal resection and reconstruction (LTRR) can be performed safely and successfully in the majority of patients. Complications—particularly those related to the airway anastomosis—are infrequent but can be devastating. Several factors, including length of resected trachea, preexisting tracheal appliance, prior tracheal resection, and medical comorbidities such as diabetes have been shown to increase the risk of anastomotic complications. Careful preoperative

planning, intraoperative technique, and postoperative care mitigate but do not eliminate this risk. Early recognition is the key to effective management of complications. Special emphasis is placed on securing a stable airway, which may in turn require a temporary endotracheal tube or airway appliance. When an anastomotic complication is addressed promptly most patients will go on to have a good outcome. However, the presence of an anastomotic complication increases the risk of perioperative mortality and long-term morbidity (i.e., need for a permanent airway appliance) substantially compared to an uncomplicated operation.

Table 1 Results of tracheal resection according to reason for tracheal resection

Variable	Overall (n=901) (%)	PITS (n=589) (%)	TEF (n=21) (%)	ILTS (n=83) (%)	Tumor (n=208) (%)	P value
Stay (d)						<0.001
Median	8	8	10	7	8	
Interquartile range	7–11	7–11	16–21	7,8	7–11	
Complications (No.)	164 (18.2)	109 (18.5)	6 (28.6)	8 (6.6)	41 (19.7)	0.11
Anastomotic complications (No.)	81 (9.0)	65 (11.0)	3 (14.3)	2 (2.4)	11 (5.3)	0.009
Death (No.)	11 (1.2)	8 (1.4)	1 (4.8)	0	2 (1.0)	0.02
Result (No.)						0.04
Good	853 (95.0)	553 (95.2)	18 (90.0)	82 (98.8)	200 (97.1)	
Tube	37 (4.2)	28 (4.8)	2 (10.0)	1 (1.2)	6 (2.9)	

PITS, post-intubation tracheal stenosis; TEF, tracheoesophageal fistula; ILTS, idiopathic laryngotracheal stenosis.

Incidence of complications

Complications following TRR and LTRR can be broadly classified as anastomotic or non-anastomotic. Anastomotic complications include formation of granulation tissue, restenosis of the trachea, varying degrees of anastomotic separation, and fistulae to surrounding structures like the innominate artery [tracheoinnominate fistula (TIF)] and esophagus [tracheoesophageal fistula (TEF)]. Non-anastomotic complication specific to upper airway reconstruction include laryngeal edema and glottic dysfunction, either with regard to phonation or swallowing.

The largest series of TRR and LTRR was published by Wright *et al.* (1). It includes 901 patients who underwent TRR and LTRR at the Massachusetts General Hospital between 1975 and 2003. The results are summarized in *Table 1*. Indications for surgery were postintubation tracheal stenosis (PITS) in 589 patients, tumor in 208 patients, idiopathic laryngotracheal stenosis (ILTS) in 83 patients, and TEF in 21 patients. Complications occurred in 164 patients (18.2%). Of these, 81 patients (9.0% of total) had anastomotic complications. LTRR was associated with more complications than TRR. The majority of patients (95%) had a good result from surgery and perioperative mortality was only 1.2% with most deaths occurring during the early years of the study period. Similar results have been reported in recent smaller series by Mutrie *et al.* (2), Bibas *et al.* (3), and Piazza *et al.* (4). Overall, rates of complications both anastomotic and otherwise have decreased from earlier series (5-7), reflecting improvement in patient selection and operative technique.

Of the 81 patients in Wright's series who had anastomotic complications, seven (1%) had granulation tissue form at the anastomosis, 37 (4%) had restenosis, and 37 (4%) had separation. The incidence of granulation tissue formation has decreased markedly from earlier series from the same institution owing to a change in surgical technique (8). Fistula formation is fortunately a rare event. Three patients developed TIF and three developed TEF. The consequences of TIF, however, are dire.

Non-anastomotic complications occur with moderate frequency following all types of tracheal resection. Wound infection requiring antibiotics with or without drainage occurs in 3–10% of patients (2). Laryngeal dysfunction either in the form of edema or vocal cord palsy increases in frequency the closer the anastomosis is to the vocal cords. Laryngeal dysfunction may also manifest as impaired postoperative swallowing, which is reported in 2–4% of patients (3). Edema requiring intervention is uncommon though precise quantification is difficult. Piazza e*t al.* reported 4 out of 137 patients (3%) who required aggressive management for suspected edema. True injury to the recurrent laryngeal nerve is infrequent (14 of 901 patients in Wright's series). Laryngeal resection increases the risk considerably. Postoperative hoarseness, however, occurs in 5% of patients (4). For most patients it is impossible to know if hoarseness is a manifestation of laryngeal edema, transient vocal cord palsy, or true nerve injury. Other serious complications such as pneumonia, myocardial infarction, and pulmonary embolism occur at similar or lower rates than those seen following other major thoracic procedures.
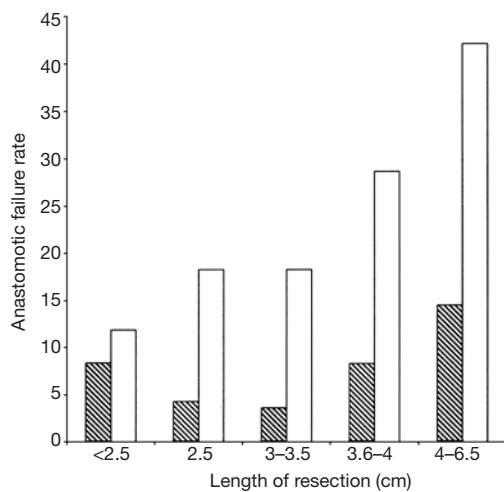
Figure 1 Anastomotic complication rate as function of length of resection in patients undergoing first resection (n=800, diagonally striped bars) and reoperation (n=101, solid bars). Lengths are presented as quintiles [Reprinted with permission (1)].

Prevention of complications

Several factors have been shown to influence the incidence of anastomotic complications following TRR and LTRR. These include indication for surgery, history of prior resection, presence of an airway appliance, medical comorbidities, and length of trachea resected. Only some of these factors can be modified; however, identifying high-risk individuals improves procedural planning and helps manage patient expectations.

Preoperatively

Institutional and individual surgeon experience has a measurable impact on outcomes following complex airway surgery. Grillo *et al.* observed that in his personal series of 280 patients the incidence of complications decreased significantly during the second half of the study period (6). The same is certainly true for the anesthesiologists who manage these complex patients in the operating room and the nursing teams who take care of them postoperatively. Tracheal surgery should therefore ideally be performed only in centers with a reasonable operative volume.

Certain patient populations should be approached with caution. In particular, patients with tracheomalacia coexisting with focal stenosis often have suboptimal results from surgery. Similarly, patients with stenosis related to

Wegener's granulomatosis are poor candidates for resection given the unpredictable and relapsing course of the disease. In both groups a permanent airway appliance should be strongly considered if necessary to maintain airway patency. Pediatric patients deserve special consideration because empiric evidence demonstrates that the juvenile trachea tolerates tension less well than that of the adult. Up to 50% of the adult trachea can be resected whereas in children that number is closer to 30% (9).

Patients undergoing resection for TEF or PITS are at significantly higher risk for complications compared to those undergoing resection for tumor or ILTS. This can be explained by a number of factors. Patients with TEF have complex pathology, chronic illness, and a substantial burden of comorbid conditions. Like patients with PITS, they also tend to have a long segment of involved trachea. Inflammation around the site of stenosis or fistula creates more peritracheal adhesions, and a tracheal appliance further complicates the picture. This makes the decision about how much trachea to resect difficult. In contrast, patients with tracheal tumors have focal pathology, minimal surrounding inflammation, and a history of prior procedures that has typically been limited to endobronchial ablation or tumor debridement. The caveat is that tracheal tumors treated with induction radiation may be difficult or impossible to manage surgically. If tracheal resection is an option, preoperative radiation should be assiduously avoided. The experience with TRR after radiation is small but available evidence suggests that the likelihood of an anastomotic complication increases considerably (10). Patients with ILTS represent a special group in whom the incidence of complications is relatively low. These patients tend to be healthy women with focal subglottic pathology amenable to short-segment resection. Anastomotic complications occur in this group at a rate of only 2.4%, compared to 5.3% for tumors, 11% for PTIS, and 14.3% for TEF.

Revision tracheal surgery is particularly challenging. Donahue (11) found that of 75 patients undergoing redo TRR and LTRR, complications occurred in 39%. This finding is supported by Wright's series, with the additional observation that the incidence of anastomotic failure increased compared to initial surgery regardless of the length of trachea resected (*Figure 1*). Revision TRR and LTRR is difficult because anastomotic tension is unavoidable: additional trachea must be resected and scarring from the previous operation limits the mobility of the remaining trachea. Unfortunately, many patients are not

candidates for reoperation because of insufficient residual tracheal length. If reoperation is attempted, at least six months should pass from the initial operation to allow time for peritracheal inflammation to resolve.

Patients with medical comorbidities are at higher risk following surgery. In particular, diabetes has been shown to increase the incidence of anastomotic complications by an odds ratio of 2.7. Diabetes is known to impair microvascular circulation and decreases perfusion to the tracheal anastomosis. Systemic steroids also impair wound healing and should be weaned prior to resection. Preoperative steroids do not prevent airway edema and should not be used to that end. Obesity has also been shown to correlate with an increase in postoperative complications. A program of weight loss and improved glycemic control prior to TRR and LTRR is of theoretical benefit.

Optimization of the patient's airway prior to TRR and LTRR is critical to the success of the operation. Preoperative bronchoscopy demonstrating abundant secretions or significant tracheobronchitis should prompt a course of inhaled or systemic antibiotics. Thorough airway assessment includes direct visualization of the vocal cords. Glottic pathology should be addressed prior to a subglottic or tracheal surgery. Emergent TRR or LTRR is essentially never indicated. Stenoses may be dilated or managed with an airway appliance placed at the level of planned resection. Tumors may be cored out or ablated. Self-expanding metal stents should be avoided because of their tendency to produce inflammation and granulations, effectively lengthening the amount of airway that should be resected. If a tracheostomy or t-tube is required the stoma should mature completely before proceeding with surgery. Likewise, preoperative decannulation is desirable but if achieved the stoma should be allowed to heal for several weeks. The impact of a tracheal appliance on postoperative complications manifests in several ways. Firstly, a tracheostomy or t-tube promotes colonization of the airways with pathogens that produce local inflammation and may influence healing. Secondly, a stoma placed remotely from the site of stenosis may cause malacia in that segment of trachea, or occasionally result in a second site of stenosis. Lastly, scarring from prior neck surgery limits mobility of the trachea and places tension on the anastomosis. These factors explain the observed twofold increase in complications associated with preoperative tracheostomy. It should be noted, though, that the need for postoperative tracheostomy is in of itself an independent risk factor (1).

Intraoperatively

Grillo and colleagues popularized a technique for tracheal resection that addresses several common postoperative concerns. Most tracheal pathology can be approached through a transverse cervical incision. When a stoma is present the skin around the area should be widely excised with the incision to decrease the likelihood of wound infection. Dissection is performed directly on the trachea to avoid the recurrent laryngeal nerves. No attempt is made to identify the nerves because doing so places them at risk. Circumferential dissection of the trachea is performed only at the level of pathology and carried a centimeter or so cephalad and caudad. This prevents disruption of the lateral blood supply to the trachea. Two large traction sutures decrease tension on the anastomosis, which is performed with interrupted absorbable sutures tied such that the knots are extraluminal. Grillo found that the transition from nonabsorbable (polyester) to absorbable (vicyrl) suture resulted in a dramatic decrease in the incidence of granulation tissue formation. Once constructed, the anastomosis is covered anteriorly with a well-vascularized muscle flap if the innominate artery is adjacent to the anastomosis. In patients who are at particularly high risk for anastomotic problems, such as those who have undergone preoperative radiation or prior tracheal surgery, buttressing the anastomosis with omentum is a reasonable alternative.

The degree of tension on the anastomosis is the most significant technical factor that influences the rate of postoperative anastomotic complications. In turn, tension correlates linearly with the length of trachea resected. Wright found that that for adult patients the incidence of anastomotic separation doubles when greater than 4 cm of trachea are removed. This trend is more pronounced for patients undergoing redo tracheal resection. Several maneuvers can be performed to reduce anastomotic tension. A suprahyoid release—first described by Montgomery in 1974 (12)—gains an additional 1–2 cm of length following upper tracheal resection and can be performed through a cervical incision. A pericardial release is more effective for lower tracheal or carinal resection and requires a separate thoracic incision. Release maneuvers are generally well tolerated and should be performed liberally if the surgeon deems the anastomosis to be under excessive tension. In Wright's series, 81 patients underwent release and 21 (25%) subsequently developed an anastomotic complication. This figure does not demonstrate a causal relationship between release maneuvers and anastomotic complications, but

rather supports the idea that an experienced surgeon's assessment of intraoperative tension is quite reliable. It is probable that most or all of those 81 patients would have had an anastomotic complication in the absence of a release maneuver.

Postoperatively

Extubation in the operating room is the goal following TRR and LTRR. If postoperative anastomotic or laryngeal edema precludes immediate extubation the patient should be temporized with a small, uncuffed endotracheal tube and returned to the operating room after 24–48 hours for a second attempt. Repeated failure should be addressed with a small tracheostomy placed at least 2 cm distal to the anastomosis. Alternatively, if the surgeon judges that timely extubation is unlikely, a tracheostomy may be placed in this location at the time of initial surgery.

The neck is maintained in gentle flexion during the initial postoperative period to prevent tension on the anastomosis. This is achieved by use of a guardian suture placed between the submental crease and presternal skin to prevent hyperextension. Some centers do not use a guardian suture with compliant patients and have found that its omission decreases length of stay (2).

Retching and vomiting are potentially catastrophic events in a patient with a fresh tracheal anastomosis given the association with sudden neck hyperextension and the potential for aspiration of gastric contents. Prevention and management of postoperative nausea, both by encouraging non-narcotic pain management and with liberal use of antiemetics, is an important part of the recovery pathway.

Voice rest is helpful in preventing laryngeal edema, particularly in patients undergoing LTRR. Patients are instructed to limit speech to no more than a whisper for the first week or so, and to avoid loud speech for several weeks after that.

Swallowing dysfunction is addressed proactively. All patients should work with a speech pathologist prior to initiating a diet and a modified barium swallow should be obtained when swallowing dysfunction is suspected. Some centers obtain such studies routinely (2).

Routine bronchoscopy is performed on all patients about one week after surgery. Direct visualization of the anastomosis is the most sensitive way to assess healing and, if necessary, initiate aggressive management of subclinical anastomotic issues. A low threshold for performing bronchoscopy earlier if concerning symptoms are present is crucial in preventing an anastomotic complication from causing significant morbidity or death. Stridor, voice changes, excessive secretions, subcutaneous air, or wound infection may all be signs of an anastomotic problem and are an indication for urgent bronchoscopy.

Management of specific complications

Granulation tissue

Granulation tissue formation occurs on a spectrum ranging from mild inflammatory changes at the anastomosis to, rarely, complete airway obstruction. This complication is seen far less frequently in the era of absorbable sutures. The time course is usually days to weeks after surgery. Obstructive airway symptoms suggest the diagnosis and bronchoscopy confirms it. The majority of patients can be managed with local debridement using the tip of a rigid bronchoscope. Injection of corticosteroids around the area of granulation following debridement may be of some benefit. Endoscopic laser has been used for patients with granulation tissue from airway stents but no data exist regarding its use in the context of an airway anastomosis. When granulation tissue becomes severe and airway obstruction is a concern, insertion of a t-tube should be considered and reoperation may ultimately be required.

Restenosis

Restenosis of the trachea may be the consequence of an anastomotic problem or be part of the natural history of the patient's underlying pathology. Patients with PITS are at highest risk for restenosis due in part to the potential for diseased trachea to be left behind at the time of initial operation. If this is the case, restenosis typically presents in the early postoperative period. For most patients, though, restenosis occurs over a period of months and is the product of tension on the anastomosis, ischemia of the cut ends of the trachea, subclinical anastomotic separation, or some combination of the above. Evaluation and dilation with flexible and rigid bronchoscopy is both diagnostic and therapeutic. Reoperation is indicated for patients in whom dilation fails to provide durable relief. A t-tube may be used to temporize patients prior to reresection or as a permanent solution for patients who lack sufficient residual trachea.

Anastomotic separation

Separation of the tracheal anastomosis may present

dramatically with loss of the airway and extremis, insidiously with wound infection, subcutaneous air or progressive stridor, or asymptomatically as a finding on routine bronchoscopy. Most commonly it occurs within the first days or weeks after surgery but more remote events have been described. Excessive tension is usually at fault. The resulting defect is most often anterior where the bulk of tension is distributed. For the patient presenting in extremis the priority is stabilizing the airway. Concomitant laryngeal edema can make this a harrowing experience. Reopening the incision at bedside and cannulating the distal airway is a measure of last resort. With the airway secure, or for the patient with a more subtle presentation, the diagnostic procedure of choice is bronchoscopy performed in the operating room. If separation is confirmed the neck is explored. When the degree of separation is small it may be sufficient to cover the defect with a muscle flap. For most patients, though, insertion of an airway appliance through the defect is indicated. A t-tube is preferred if the upper airway remains patent. More commonly, anastomotic separation is accompanied by significant laryngeal edema that obstructs the upper airway and mandates placement of a tracheostomy. Immediate revision of a tracheal anastomosis after dehiscence should generally be avoided; however, for a structurally normal anastomosis that is pulled apart by sudden violent neck extension as with coughing or retching, one might reasonably attempt suture repair.

For patients with a small anastomotic defect and minimal or no symptoms it may be possible to avoid re-exploration. Antibiotic therapy with or without local drainage is instituted to control local contamination, voice rest and neck flexion are continued, and the anastomosis is allowed to heal with time. Hyperbaric oxygen therapy (HBOT) has been used to good effect in these situations. Laboratory studies performed in rats demonstrate improved tracheal healing associated with HBOT (13). Stock *et al.* (14) reported on five patients with minor anastomotic separation after TRR performed at Massachusetts General Hospital who were treated with HBOT (2 atmospheres for 90 minutes for an average of 13 sessions). All were able to avoid subsequent revision of the anastomosis over a follow-up period of 1 to 3 years. One patient required debridement for granulation tissue and another required tympanostomy tubes to tolerate HBOT. Further studies are needed but sufficient evidence exists to support the use of HBOT for selected patients with minor anastomotic complications.

Wound infection

Cervical wound infections occur rarely but must be promptly diagnosed and treated—both to prevent erosion into the anterior anastomotic area and in case the infection is the first sign of a brewing anastomotic problem. Redness, drainage and increased incisional pain suggest a wound infection. Cough, increased sputum production, or stridor associated with a wound infection is suspicious for an underlying anastomotic. Management consists of opening and culturing the wound. A CT scan is done to look for extraluminal air, undrained collections and other signs suggestive of an anastomotic problem. If there is a reasonable chance of an anastomotic problem, urgent bronchoscopy should be done. If there is a partial anterior dehiscence associated with a wound infection it may be addressed by placing a small temporary tracheostomy and properly draining the surrounding infection. Most patients will heal quickly without need for major revision.

TIF and TEF

Fistula formation between the anastomosis and the innominate artery is often a fatal event. Two of the three patients who developed TIF in Wright's series subsequently died. TIF forms as a result of anterior separation of the anastomosis causing soft tissue inflammation and infection that in turn erodes into the innominate artery. Dissection around the artery at the time of resection exposes it and places it at risk for involvement in a fistula should anastomotic separation occur. Hemoptysis is the cardinal sign of TIF. A sentinel, small-volume episode of hemoptysis may precede a life-threatening event. Airway symptoms suggestive of anastomotic separation are typically present. Small-volume hemoptysis in a stable patient may be investigated with a CT-angiogram prior to bronchoscopy. Massive hemoptysis mandates immediate return to the operating room. Exposure of the innominate artery requires a partial or complete sternotomy. The artery is ligated and divided and the cut ends are separated from the infected field with healthy tissue. The airway defect is then addressed in the same fashion as described above. Dividing the artery should not result in cerebral ischemia provided that the bifurcation of the right subclavian and carotid arteries remains intact.

Fistula from the anastomosis to the esophagus is also rare but can be a significant source of morbidity. TEF occurs in the context of a posterior separation of the anastomosis. The

esophagus becomes involved either through direct injury during tracheal dissection or secondarily from the resulting infection. Patients may present months after surgery with post-prandial cough, pneumonia, or obstructive upper airway symptoms. Barium swallow and bronchoscopy confirm the diagnosis. TEF is managed in delayed fashion. The airway is controlled with a tracheostomy or t-tube and the patient is fed enterally until operative conditions improve. Definitive management includes revision of the airway anastomosis, two-layer repair of the esophageal defect and interposition of healthy tissue. Occasionally it may be sufficient to repair the esophagus alone and allow a small defect in the airway to heal over time. In Wright's series, all three patients who developed TEF ultimately had a good outcome.

Laryngeal edema

Laryngeal edema causing obstructive airway symptoms is more common following laryngeal resection. For high laryngeal resection postoperative swelling is the rule. Patients present with voice changes described as "husky". Stridor is sometimes present as well. Bronchoscopy is usually diagnostic and importantly rules out concomitant anastomotic separation. Mild cases are addressed with steroids, diuretics, nebulized epinephrine, and head elevation. If loss of the airway is a concern the patient should be intubated with a small, uncuffed endotracheal tube. Edema that fails to resolve after a few days of intubation and medical therapy is an indication for tracheostomy.

Recurrent laryngeal nerve palsy

Recurrent laryngeal nerve injury following TRR and LTRR is rare if proper technique is observed and the nerves are kept from entering the surgical field. However, some degree of postoperative hoarseness is relatively common and may be the result of mild laryngeal edema or transient nerve palsy brought on by inflammation or traction. Hoarseness should be investigated with direct laryngoscopy but even if immobility of one of the vocal cords is demonstrated the potential for recovery cannot be known. Given this ambiguity, at least six months should transpire before medialization laryngoplasty is considered. Temporary injection of the cord is indicated if there is objective evidence of ongoing aspiration. In the interim, patients with suspected nerve injury should work closely with a speech pathologist to improve swallowing and phonation.

Swallowing dysfunction

All laryngeal resections produce some degree of edema that contributes to postoperative swallowing dysfunction. Additionally, a suprahyoid release impairs normal motion of the larynx during swallowing and extended trachea resection may do the same by tethering the larynx and preventing normal elevation. Some component of recurrent laryngeal nerve palsy may be at play for some patients. Older patients tolerate modest swallowing dysfunction poorly. Fortunately, improvement almost always occurs with time and dedicated work with a speech pathologist. Rarely patients require placement of a gastrostomy tube to maintain nutritional intake during this period.

Outcome after an anastomotic complication

Even in the presence of an anastomotic complication results following TRR and LTRR are good. Of the 81 patients who developed an anastomotic complication in Wright's series (37 separation, 37 restenosis, 7 granulation tissue formation), 41 (51%) ultimately had a satisfactory airway. Multiple dilations and temporary airway appliances were necessary in 2 and 23 patients, respectively. Sixteen patients required reoperation but all ended up with a satisfactory result. The remaining 40 patients progressed to needing a permanent tracheostomy (14 patients), t-tube (20 patients) or died as a result of the anastomotic complication. Three patients died from anoxic injury, two from TIF, and one from mediastinitis. Death in the absence of an anastomotic complication occurred in only five patients (0.6%). An anastomotic complication was associated with a thirteen-fold increase in mortality. Median hospital stay was also extended, from 8 days without an anastomotic complication to 14 days with one.

Conclusions

Complications following tracheal surgery are not common but must be addressed promptly and effectively when they arise to prevent major morbidity. Stabilization of the patient's airway, evaluation with bronchoscopy, and use of a temporizing airway appliance are all important components of the management of airway complications. Most patients with an anastomotic complication respond well to aggressive management and will go on to have a good outcome.

Acknowledgements

Footnote

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Techniques of protection and revascularization of the bronchial anastomosis

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Abstract: Airway anastomosis has been traditionally considered at risk for the onset of complications, particularly dehiscence with consequent infection and erosion in the adjacent vessels. Although the modifications and improvements of the surgical technique has contributed to reduce the incidence of complications, the protection and revascularization of the anastomotic site is still considered mandatory at many centers Many techniques have been proposed for encircling the bronchial anastomosis.

Keywords: Sleeve resection; bronchial anastomosis; lung cancer

Airway reconstructions with end-to-end anastomosis are usually performed in case of bronchoplastic procedures such as sleeve lobectomy (1-3) or sleeve pneumonectomy with carinal resections (4) and lung transplantation (5,6). This anastomotic site has been traditionally considered at risk for the onset of complications, particularly dehiscence and erosion in the adjacent pulmonary artery (PA). Although the surgical technique has been modified (5) and the incidence of complications has progressively decreased, many groups still consider mandatory the protection and revascularization of the anastomotic site. On the other side, there are reports supporting that unprotected bronchial anastomosis is safe even after induction chemotherapy (7) and lung transplantation (8).

Many techniques have been proposed for encircling the bronchial anastomosis. Pleural, pericardial and thymic flaps have been used successfully; however, the use of muscle flaps, particularly the intercostal muscle flap, is preferable since it contains its own blood supply and is less prone to shrinkage and fibrosis (9). These techniques have been also used to reinforce the bronchial stump after lobectomy and pneumonectomy (9,10).

Intercostal pedicle flap

The preparation of this flap is usually performed before entering the chest, to avoid crushing with the rib retractor, which is inserted only when the flap is ready and placed in the posterior aspect of the chest (11-14). The periosteum of the upper rib of the intercostal space involved at thoracotomy is incised and separated from the bone along with the underlying intercostal muscle. A sufficient flap of parietal pleura is mobilized upward by finger dissection along with the intercostal muscle. The preservation of the periosteum is crucial to avoid injuring the intercostal bundle. The upper part of the flap is now ready. The intercostal muscle is now incised at the level of its insertion of the underlying rib preserving a flap of pleura also on this side. At this level it is not required to incise the periosteum that remains in place. This maneuver allows reducing the thickness of the flap and this layer of muscular fibers left in place helps to fill the gap between the ribs when closing the chest, preventing the onset of subcutaneous emphysema in case of air leaks. Thickness is an important issue: a thin flap slides more easily between the bronchus and the PA without

any compression of the vessel. Only at this point the rib spreader can be inserted and the flap is divided anteriorly, at the level of the costo-chondral junction, ligating the extremity; a silk tie is left attached to this extremity of the flap to improve the subsequent sliding maneuver.

After completing the bronchial anastomosis, a right angle clamp is slid between the PA and the bronchus and the silk tie is grasped and withdrawn backward with the flap. The intercostal muscle is gently twisted leaving the pleural surface in contact with the bronchus. The pleura is secured to the bronchus with interrupted absorbable 4-0 sutures.

The thoracoscopic preparation of an intercostal muscle flap has been reported (15), although in that case it was used to reinforce a standard lobectomy bronchial stump and the service thoracotomy was a little too long for the current thoracoscopic lobectomy standards (8 cm). Robotic preparation of the intercostal muscle flap has also been described by Lazzaro in 2013 (16).

This preparation of the intercostal muscle is advisable in case its need it is anticipated preoperatively; if not used, the flap can be placed again between the ribs while closing the thoracotomy. However, there are cases in which the need of a bronchial sleeve resection requires intraoperative confirmation. In these situations, the surgeon would add operative time preparing an unnecessary flap or have a useless intercostal muscle crushed by the rib spreader, requiring mobilization of other flaps. In such patients it might be advantageous to prepare the segmental nondivided intercostal muscle flap during thoracotomy (17,18). This technique has been described to decrease postoperative pain after thoracotomy (18,19). According to this technique, mobilization from the rib is required only at the level where the retractor is placed; it takes only a few minutes and it makes the intercostal muscle available in case on an unexpectedly complicated surgical resection. If the flap is required mobilization can be completed as previously described. If the flap is not required the minimal mobilization allows easy closure of the chest.

Assessment of the quality of the pedicled intercostal muscle flap could be useful before using it. For this purpose indocyanine green fluorescence (ICG) have been used (20); after injection ICG fluorescence imaging is assessed with a near—infrared camera system visualizing the presence of poor perfused areas within the pedicle.

No early complications have been recorded with the preparation and use of the intercostal muscle pedicle. Ossification of the pedicle is a well-known phenomenon (11,21,22) with uncertain clinical implications. In previous reports we described this phenomenon without any clinical significance (11,23), in line with other authors (24). However, other authors have reported the occurrence of a bronchial stricture as a consequence of ossification (18,25). In an experimental study Fell (22) showed that cauterization of the periosteum with 30% silver nitrate contributes to reduce the amount of calcification; he suggested (26) loose wrapping of the pedicle around the bronchial anastomosis. Harvesting with a cautery so it is devoid of periosteum avoid calcification (27,28).

Pleural flaps

Pleural flaps have been initially described to reinforce the pneumonectomy (29) and lobectomy (30) stumps and subsequently have been interposed between the bronchial anastomosis and PA in sleeve lobectomy (31). The pleural flap is harvested after thoracotomy; a triangular incision with the medial base of the flap one-third the width of the distal side; the proximal side arrives close to the mediastinum. The edges of the flap are gently lifted and a plane is dissected under the parietal pleura to its base. The flap is subsequently folded around the bronchial anastomosis and fixed to the bronchus with absorbable suture.

Pericardial flaps

Pericardial flaps are used in a great number of situations: to protect tracheal or bronchial anastomoses, including sleeve resections (31-35), to repair recurrent tracheoesophageal fistulas (36,37), and to repair congenital tracheal and esophageal stenosis (38). To prepare the flap, the pericardium is incised avoiding injuring the pericardiophrenic bundle and it is rotated to wrap the anastomosis or protect the suture line. The pericardial defect usually does not require closure unless pneumonectomy is performed.

Pericardial fat pad graft

This pedicle is usually employed to reinforce and protect bronchial stumps since it is difficult to obtain a graft of adequate length to wrap a bronchial or tracheal anastomosis. It was described first by Brewer in 1953 (39). The pedicle is usually freed off the pericardium based on the middle pericardial and musculophrenic branches of the internal mammary artery (9). The anastomotic vessels to the pericardiophrenic branch anteriorly and musculophrenic artery inferiorly are divided (9). The graft consists of the

overlying mediastinal pleura, adipose tissue and blood vessels and can be fixed in its final position. Alternatively, a shorter graft can be harvested by the antero-superior fat pad, where the blood supply originates from the superior pericardial branch of the internal mammary artery and anterior mediastinal vessels.

Pedicled pericardiophrenic graft

This graft is useful only in patients undergoing pneumonectomy, to protect the bronchial stump, or to wrap the anastomosis after carinal pneumonectomy. It consists of mediastinal pleura, phrenic nerve, and the adipose tissue surrounding the pericardiophrenic bundle. This pedicle is mobilized upward dividing the vessels above the diaphragm (9).

Omentum

The omentum is extremely useful to protect and reinforce any anastomosis and suture within the chest (40-43). It can be easily mobilized with a small incision and transposed within the chest. Its use to wrap the bronchial anastomosis was crucial in the early days of lung transplantation to solve the anastomotic problems.

The omentum derives its blood supply from the right and left gastroepiploic vessels forming an arcade within the fat tissue. The length of the omentum is about 3 cm and the width is about 40 cm. The omentum can be further mobilized by dividing the attachments with the transverse colon, with a pedicle based on the right gastroepiploic vessels, freeing the arcade from the stomach. By dividing the left gastroepiploic vessels the length of the flap is increased so much that it could reach the neck.

The omentum with its length and adequate vascular supply provides enough soft tissue for coverage and wrapping, it functions also in infected fields, it provides fibroblasts and healing and enhances neovascularity.

Peribronchial mediastinal tissue

This tissue is specifically used to cover the bronchial anastomosis during lung transplantation by approximating the peribronchial donor and recipient tissue. This provides adequate protection of the bronchial anastomosis and separates it from the vascular side in case of anastomotic breakdown (4,44).

Overall, many flaps have been used to protect airway anastomosis after reconstruction. The selection of the most appropriate is related to the anatomic characteristics of each patient and the type of surgical procedure. The critical point, once selected the most appropriate flap, also on the base of the surgeon preference, is to harvest and maintain it well vascularized and vital. This in the only condition, along with an adequate length, to provide an effective coverage and protection of the anastomosis.

Acknowledgements

Footnote

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A novel surgical method for acquired non-malignant complicated tracheoesophageal and bronchial-gastric stump fistula: the "double patch" technique

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Background: To manage the acquired benign complicated tracheoesophageal fistula (TEF) and bronchial-gastric stump fistula (BGSF) are clinical technical challenge. The purpose of this study is to retrospectively review a surgical "double patch" technique in treating nonmalignant complicated TEF and BGSF, and then clarify the long-term curative effect of the technique.

Methods: Clinical records of 30 patients with non-malignant complicated TEF and BGSF treated by "double patch" technique in Tangdu Hospital between August 2004 and August 2014, were analyzed and summarized retrospectively.

Results: Thirty patients (19 males and 11 females) underwent "double patch" surgical repair of acquired benign complicated TEF and BGSF. The median age of the patients was 40.2±21.1 years. The most common causes were the following: TEF [22], BGSF [8]. Post-intubation injury [6], trauma [5], foreign body and stents [10], complications from prior esophageal surgery [8], and caustic ingestion [1]. The follow-up was completed for 24 months in all the patients (100%). The operative mortality was 0% (0/30). Twenty-six patients (86.7%) recovered uneventfully while four patients (13.3%) exhibited some major complications in the perioperative and postoperative periods. One patient (3.3%) developed recurrence of tracheal fistula *in situ*, two patients (6.7%) showed pneumonia, and one patient (3.3%) developed fistula esophageal anastomosis. All the 30 patients resumed oral intake finally.

Conclusions: The double patch technique is an effective and safe method to repair the acquired non-malignant complicated TEF and BGSF.

Keywords: Tracheoesophageal fistula (TEF); bronchial-gastric stump fistula (BGSF); double patch

Introduction

Acquired non-malignant fistula between the airway and upper gastrointestinal tract is a rare but challenging clinical issue (1). Patients with this condition have little chance of self-recovery. Abnormal communications between the airway and upper gastrointestinal tract lead to continuous contamination of the tracheobronchial tree and repeated respiratory infections. In the absence of timely intervention, patients may die of respiratory failure or malnutrition within 3–4 months

(2,3). The etiology of the fistula includes complications of mechanical ventilation, indwelling on tracheal or esophageal stents, complications from prior tracheal or esophageal surgery, granulomatous mediastinal infections, trauma, iatrogenic injuries, and caustic ingestion (1). Acquired non-malignant complicated tracheoesophageal fistula (TEF) and bronchial-gastric stump fistula (BGSF) are characterized by a large fistula (≥1 cm), severe inflammation, high rate of postoperative death and recurrence, hard to perform stent placement, need for segmental tracheal or bronchial resection, or primary anastomosis of esophageal and tracheal defect that cannot been surgically repaired (4,5).

Different approaches have been proposed to treat the acquired non-malignant TEF and BGSF. The currently available treatments include minimally invasive procedures and surgeries. Previous studies have shown varying levels of success in the use of minimally invasive procedures in patients with early detection, small fistula (<1 cm), and mild local infection. Some of these methods were covered stent placement, cardiac septal occlusion, chemical cautery, injection of Bioplastique®, histoacryl glue, glutaraldehyde crosslinked (GAX) collagen, calcium hydroxylapatite (CaHA), and Tisseel® fibrin glue (6-12). The minimally invasive procedures are advantageous because of ease of handling, simplicity, and small trauma; however, they have disadvantages of increased postoperative complications and high recurrence rate (6,13,14). The respiratory tract resection combined with end-to-end anastomosis is suggested by some surgeons to treat patients with complicated fistula (≥1 cm), severe local infection, and tissue edema. However, this method has the following limitations: time-consuming and complex procedure, increased surgical trauma, complications, and high mortality. Moreover, the length of the respiratory tract that can be removed is limited, which adds to the disadvantages of the surgery. Although it is an alternative to the complex surgical procedure of respiratory tract resection, using autologous muscle flap, pericardium, allogeneic pericardium, and other materials (AlloDerm patch) as the flap to repair the fistula is associated with disadvantages such as insufficient blood supply, limited available material for the flap repair, allograft rejection, high recurrence rate, and the need for separating surrounding tissues from the fistula (15,16). Previous studies have reported that using a neo-membranous airway with the single-layer posterior esophageal wall or simultaneously using a pedicled muscle flap to repair the fistula is capable of closing the large TEF (17-19). This method has some advantages such as the flap can be obtained locally, there is

no allograft rejection, separation of the surrounding tissues from the fistula is not required, removal of the respiratory tract is not necessary, and a muscle flap can resist the high pressure in the airway. However, for patients with a large fistula, severe local infection, tissue edema, and fragile tissues around the fistula, the single-layer esophageal flap only may not resist the high pressure in the airway, which will lead to the recurrence of fistula and tracheal stenosis (17). In addition, using a pedicled muscle flap to resist the high pressure in the airway is a complicated procedure, for which the availability of material is limited, and the blood supply cannot be certain.

Whether the acquired non-malignant complicated TEF and BGSF can be closed safely and efficiently without a pedicled muscle flap, requires further investigation. Herein, we described a novel "double patch" technique for the repair of the trachea, which uses the neomembranous esophageal walls of double layers to close the defect of the trachea or bronchus (4). We retrospectively reviewed and assessed the long-term outcomes of 30 patients with acquired benign complicated TEF and BGSF at our hospital between August 2004 and August 2014.

Methods

Clinical data

We reviewed the medical records of all patients with TEF and BGSF in the Department of Thoracic Surgery, Tangdu Hospital Affiliated to the Fourth Military Medical University, Xi'an, Shaanxi, China between August 2004 and August 2014. The duration of follow-up was 24 months. Diagnosis of the TEF and BGSF were established using upper gastrointestinal endoscopy, bronchoscopy, or upper gastrointestinal barium series. Patients who were suspected with a fistula on a computed tomography (CT) scanning of the chest were excluded if the fistula was not proven by one of the methods mentioned above (2). Patients with malignant and congenital TEF were excluded from the present study. Finally, 30 patients who underwent surgical management for acquired benign TEF and BGSF during this span (*Figure 1*) were included in the survey. The length of defects on the membranous region of the trachea and bronchus ranged from 1–5 cm. The baseline characteristics of 30 patients were recorded (*Table 1*). The study protocol was approved by the Regional Ethics Committee for Clinical Research of the Fourth Military Medical University (Number/ID: TDLL-201512-019).
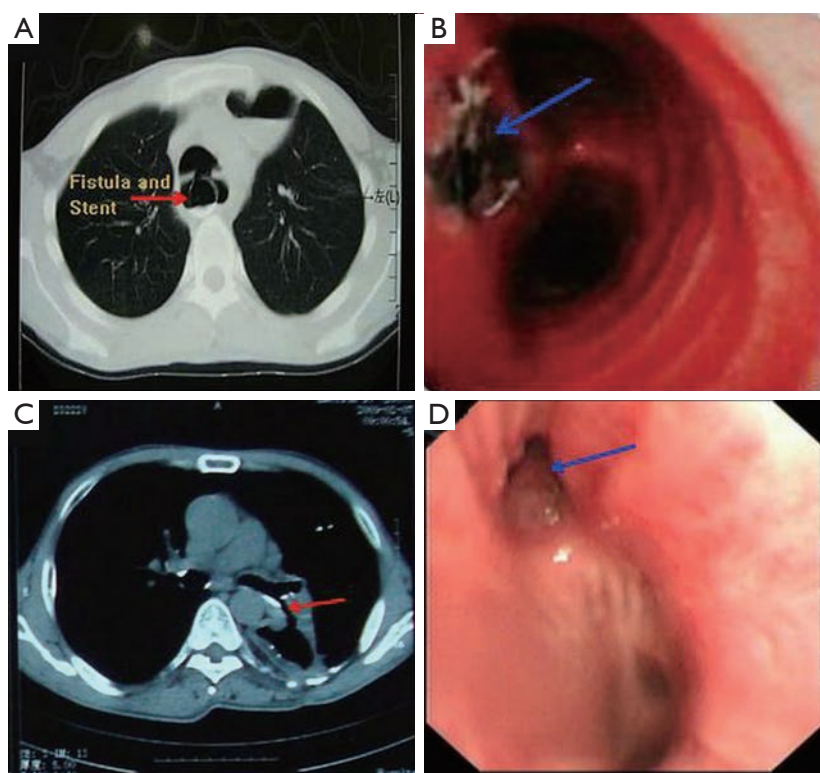
Figure 1 Computed tomography (CT) scanning and bronchoscopy of the fistula. (A,B) The CT scanning and bronchoscopy showed that the tracheoesophageal fistula (TEF), which was attributed to the esophageal stent (arrow: the fistula and the esophageal stent); (C,D) the CT scanning and bronchoscopy showed the bronchial-gastric stump fistula (BGSF) (arrow: the fistula).

Table 1 Patient characteristics

Characteristics	No. of patients (n=30)
Age (mean ± SD), years	40.2±21.1
Gender (male:female)	19:11
Type (n)	
TEF	22
BGSF	8
Etiology (n)	
Post-intubation injury	6
Trauma	5
Foreign body and stents	10
Complications from prior esophageal surgery	8
Caustic ingestion	1

TEF, tracheoesophageal fistula; BGSF, bronchial-gastric stump fistula.

Operative techniques

The surgical procedure for all the patients was performed by an identical team, which included a senior thoracic surgeon, an anesthetist, and two junior thoracic surgeons. An endotracheal tube for ventilation was inserted before surgery. When the defect was located on the main trachea or up the arch of azygos vein, the double-lumen endotracheal tube balloon was sent into the main bronchus to ensure ventilation, and a posterolateral thoracotomy was performed through the right 4th or 5th intercostal space. In the case of the defect located on the main bronchus, the double-lumen endotracheal tube balloon was sent into the contralateral main bronchus to ensure ventilation, and a posterolateral thoracotomy was performed through the fifth intercostal space or the prior thoracic incision.

The esophagus or gastric stump was not separated from the fistula. The thoracic segment of the esophagus was transected away from the proximal and distal edge of the fistula to approximately 1–2 cm. Then, a longitudinal
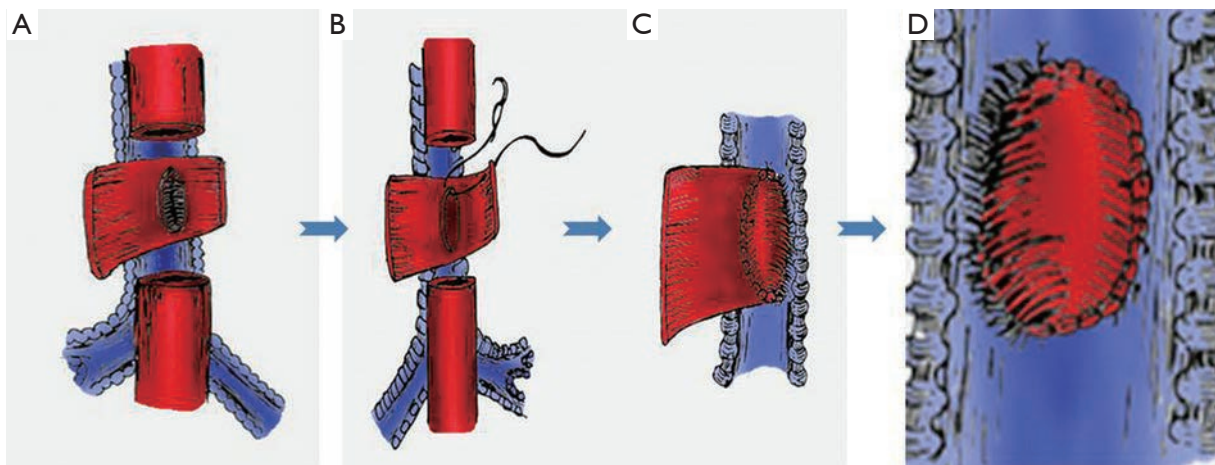
Figure 2 "Double patch" technique for tracheoesophageal fistula (TEF). (A) Two patches without esophageal mucosa were formed, a long one and a short one, on the either side of the fistula; (B,C) the short patch was sutured to the edge of the fistula; (D) the short patch was covered with a long patch.

incision was made to split open the esophageal lumen along the longitudinal axis of the esophageal posterior wall away from the left edge of the fistula by approximately 2–2.5 cm. Two esophageal patches were formed, a long one and a short one, on either side of the fistula (*Figure 2A*) (4). Subsequently, the mucosa of the patches was cauterized. The short patch was sutured to the edge of the fistula with 3-0 absorbable interrupted full-thickness sutures, which closed and buttressed the fistula completely (*Figure 2B,C*). The short patch was covered with the long patch (*Figures 2D*). Based on the same principle, a conformal incision was made on the wall of the gastric stump to form two patches similar to that of the BGSF: above and below the fistula (*Figure 3A,B*). Subsequently, the mucosa of the patches was cauterized. The short patch was sutured to the edge of the fistula with 3-0 absorbable interrupted full-thickness sutures, which closed the fistula completely (*Figure 3C,D*). The short patch was covered with the long patch (*Figure 3E*).

In the same stage, the stomach was mobilized through the opened diaphragmatic hiatus or by laparotomy, preserving the right gastroepiploic vessels and the epiploic arcade. Subsequently, the stomach was tubed and pulled up into the thorax, and an esophagogastric anastomosis was performed with a tubular anastomat. Alternatively, gastrorrhaphy was conducted (*Figure 3F*). The chest was closed after insertion of two intercostal drains.

Results

The duration of follow-up was 24 months, and no mortality

was observed in this cohort of 30 patients. All of them finally resumed oral intake.

Twenty-six patients (86.7%) who underwent the double patch technique showed complete healing, without significant complications occurring in the postoperative period. The success of the repair was examined using a bronchoscope; no remarkable swelling of the patch and stenosis was noted (*Figure 4*).

In one patient (3.3%), with the recurrence of tracheal fistula (3.5 cm) *in situ* at postoperative 2nd week, tracheal intubation was performed for assisting mechanical ventilation, and nasogastric nutrition was operated immediately. The patient was managed conservatively. The patient was treated with tracheal resection, and the tracheal continuity was maintained with end-to-end anastomosis when the physical condition reached surgical requirements. Bronchoscopy during the follow-up showed complete healing of the fistula.

Two patients (6.7%) presented complication (pneumonia) in the perioperative and postoperative period, which was mainly caused by TEF and BGSF. Both the patients were managed conservatively and were administered antibiotics and bronchoscopic suctioning. They were treated for 10 days, and pneumonia was cured completely.

Failure to resume oral intake in one patient (3.3%) was due to fistula esophageal anastomosis, which contributed to empyema. Nasogastric nutrition and closed thoracic drainage were performed immediately. The patient was managed conservatively and treated for 1 month. Esophagoscopy showed complete healing of the esophageal
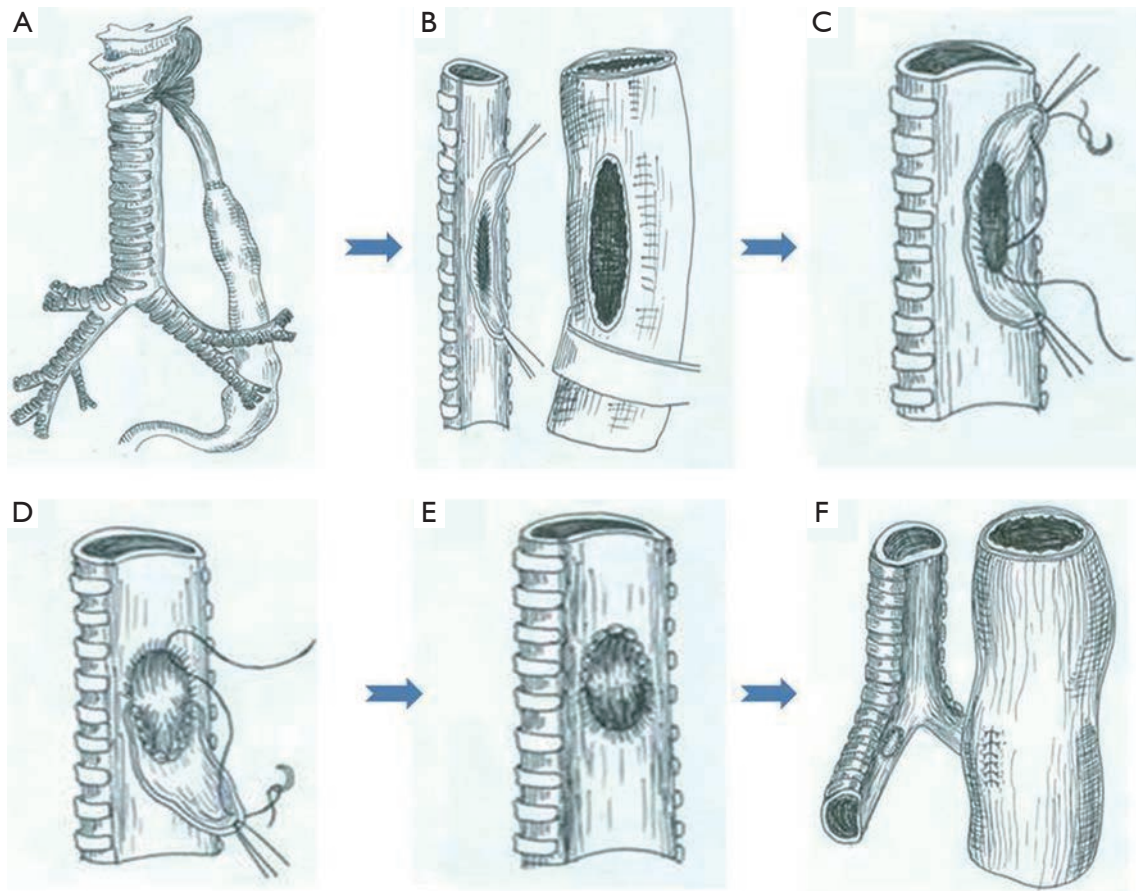
Figure 3 "Double patch" technique for the bronchial-gastric stump fistula (BGSF). (A) Left BGSF was formed after gastric tube or whole stomach interposition for esophageal substitution; (B) a conformal incision was made on the wall of the gastric stump to form two patches, a long one and a short one, above and below the fistula; (C,D) the short patch was sutured to the edge of the fistula by interrupted full-thickness suture; (E) the fistula was closed completely, and the short patch was covered with the long patch; (F) gastrorrhaphy was performed immediately.
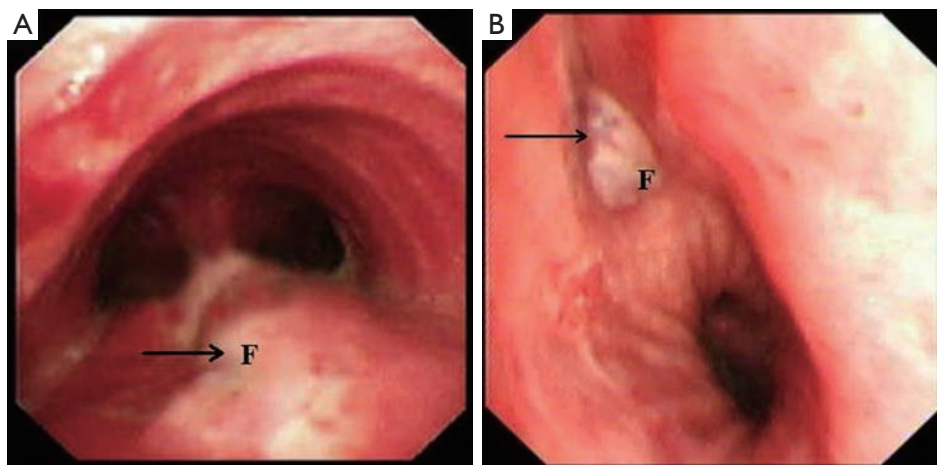
Figure 4 Tracheoesophageal fistula (TEF) (A) and bronchial-gastric stump fistula (BGSF) (B) were checked and verified by bronchoscopy on the postoperative 7th day. F, fistula.

fistula, and oral intake was restored immediately.

Discussion

The present study aimed to retrospectively summarize and analyze patients over a longer follow-up period than a previous study (4), in order to verify that "double patch" technique was an effective and safe surgical method to treat non-malignant complicated TEF and BGSF.

Herein, we overlapped neo-membranous esophageal walls of double layers to repair the airway fistula. This technique created a firm and mucosa-free patch to resist the high pressure in airway without the reinforcement of the pedicled muscle flap. Any significant swelling of the tracheal patch and stenosis was not observed in the postoperative examination by bronchoscopy. Thus, our results provided strong evidence that "double patch" technique is a reliable method to treat acquired non-malignant complicated TEF and BGSF.

In this retrospective study, thirty patients who underwent the double patch technique were enrolled. Twenty-six patients showed complete healing and did not present any major complications in the postoperative period. However, one patient showed the recurrence of fistula *in situ* at postoperative 2nd week. One explanation may be that the esophageal blood supply may be disturbed and destroyed. Because of patient suffering from caustic ingestion may contribute to esophageal stenosis, and using esophageal stent for more than 6 months led to TEF, which may lead to insufficient blood supply for the double patches. Consequently, the patient was at a risk of ischemic necrosis and recurrence of fistula. Hence, for patients with insufficient blood supply of the esophagus, the length of double patches should be sufficient (away from the proximal and distal edge of the fistula to approximately 2–2.5 cm), and the cauterization should not destroy the esophageal muscular layer, thereby avoiding damage to the blood supply.

The gland in esophageal mucosa and submucosa can secrete a large amount of mucoprotein, which resists hydrogen ion and pepsin (20). In this study, the esophageal mucosa was cauterized, which might avoid the mucoprotein secretion by the mucosal gland. Because of a large amount of mucoprotein accumulated between the two patches may constrict the airway, which may contribute to stenosis of the airway. Therefore, the esophageal mucosal gland should be completely removed in the "double patch" technique. However, this piece of evidence needs to be investigated and proved further.

Additionally, based on the results of our previous study (4) and the present study, the "double patch" technique exhibit the following features: (I) there is no need to separate the fistula; (II) the part of the esophagus with the defect could be used to repair the fistula; (III) the tracheal defect could be repaired with an esophagus segment without mucosa; (IV) the esophageal segment adhering to the fistula should be tighter; (V) a pedicled muscle flap is not required in this technique as the tracheal wall is reinforced with two patches to resist the airway pressure; (VI) reconstruction of the digestive conduit is necessary; and (VII) there is a low risk of recurrence.

Importantly, some of the procedure-related challenges, such as morphological and pathophysiological changes, structural as well as functional changes of double patches, and the postoperative effect of with or without mucosa of patches on the "double patch" technique remain unclear. Thus, animal models are essential to investigate these challenges, which will lay the theoretical foundation of the technique.

Conclusions

In summary, the "double patch" technique is a safe and effective method to repair the acquired non-malignant complicated TEF and BGSF.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was approved by the Regional Ethics Committee for Clinical Research of the Fourth Military Medical University (Number/ID: TDLL-201512-019).

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Tracheal replacement

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Abstract: Non-malignant and malignant obstruction of the tracheal airway causes significant morbidity and mortality. With increased use of artificial airways, benign and iatrogenic complications are increasing. A tracheal stenosis that is less than 5 cm in length can be resected with end-to-end anastomosis. Longer tracheal lesions can be treated in a palliative way by placement of a stent to secure airway lumen patency. The management of tracheal defects is an evolving field. Tracheal transplantation and tracheal regeneration may bring major treatment advances to cases with long-segment tracheal involvement. This review examines the current possibilities and future prospects in the area of tracheal transplantation and regeneration.

Keywords: Trachea; transplant; revascularization; regeneration

Immediate repair of long-segmental defects

Prosthetic tracheal repair

In recent years, most synthetic materials used for tracheal replacement have been tested in experimental animal research. From these studies, it became clear that definitive prosthetic replacement of the airway wall is not possible (1). To date, nearly all surgical prostheses that have been successful were observed in potentially sterile mesenchymal tissues. No example of successful prosthetic repair can be cited in the respiratory or gastrointestinal tract. The internal site of the airway tract belongs to the outside world, and bacterial contamination at the interface between the airway and prosthesis prevent its in-growth (*Figure 1*). The complications of wound breakdown at the anastomoses can be temporarily delayed by wrapping the prosthesis in vascularized tissue, mostly transposed omentum.

Palliative treatment of long-segmental defects

Long-segmental tracheal defects, which result after removal of malignant tumors are extremely rare. The only possibility for immediate reconstruction of these defects is to reduce the length of the defect by inserting a silicone stent, which is sutured to the upper and lower margins of the defect. A free fasciocutaneous skin tube (lateral thigh flap, radial forearm flap) can be used to wrap the silicone stent as a temporary closure (*Figure 2*) (2).

Tracheal allotransplantation

Introduction

The trachea is one of the few organs that are exceptionally difficult to transplant because of the technical difficulty to restore the blood supply to the graft. The blood supply of the 12 cm-long trachea depends in its entirety on small blood vessels branching out into numerous even smaller vessels, each of them subsequently penetrating the trachea in between the cartilage rings to provide blood supply to segments of the mucosal lining. If a part of the trachea is removed from the airway, all blood supply is interrupted. The removed
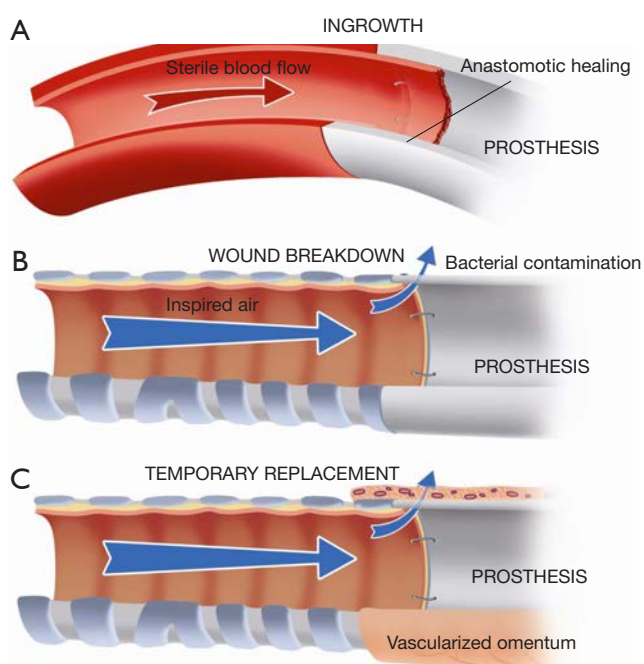
Figure 1 Prosthetic replacement: airway versus vascular conduits. (A) Blood vessel prosthesis. Endothelialization of the luminal surface of vascular grafts occurs only 1 to 2 cm into the graft from the anastomotic site. These endothelial cells are derived from adjacent, native endothelium and they enable the anastomosis to heal; (B) airway prosthesis. In the respiratory tract, the flow of inspired air will lead to bacterial contamination and wound breakdown at the anastomosis. The respiratory epithelium will not grow over the prosthesis-airway anastomosis; (C) airway prosthesis wrapped in vascularized tissue. A prosthesis may act as a temporary airway stent when it is wrapped by well-vascularized tissue (e.g., omentum). The vascularized tissue around the prosthesis may temporarily avoid the complications of wound breakdown at the anastomotic sites.

part of the trachea cannot survive, even if it were to be placed back into the airway straightaway (*Figure 3*). Our group has a 20 year-long research record in the field of tracheal revascularization and holds a leading position in the development of tracheal transplantation by means of vascularized segmental units.

A tracheal transplant may be necessary to repair surgical defects of the laryngotracheal airway tract that are unsuitable for segmental resection and autologous tissue repair. With the exception of some anecdotal, poorly documented cases performed without blood supply restoration (3) or immunosuppressive medication (4), no clinical tracheal allotransplants have been transplanted

orthotopically as an isolated composite tissue graft. In tracheal allotransplantation, it is important to deal with both immunosuppression and indirect revascularization in a heterotopic position. The first documented preserved viability of a heterotopically revascularized allotransplant was published by Klepetko *et al.* in 2004 (5). The graft was revascularized in the omentum of a patient who underwent lung transplantation from the same donor. Ultimately, the trachea transplant was not used, but its viability was documented for at least 60 days.

The first documented revascularized tracheal allotransplant to be reported was published in 2010 (6).

Our approach to tracheal heterotopic revascularization, orthotopic transplantation, and withdrawal of immunosuppressive medication is based on a series of six cases (*Figure 4*) (7). For tracheal allotransplantation, we consider a "good match" to mean that the donor is of the same blood group as the patient.

Surgical technique

Revascularization of the trachea is the first step towards successful tracheal transplantation. The typical arterial and venous blood supply, consisting of several small tracheo-esophageal branches, does not enable direct tracheal transplantation. Currently, the only reliable way to achieve tracheal revascularization is to wrap the isolated trachea with a well-vascularized soft tissue flap perfused by a vascular pedicle, which then allows for transfer of the revascularized trachea to an airway defect. The forearm fascia flap pedicled on the radial artery and vein has proven to be reliable for tracheal revascularization (7). It is important to have complete immobility between the trachea and the surrounding recipient's vascular bed to obtain a fast revascularization of the blood vessels of the tracheal adventitia (*Figure 5*).

Revascularization has to be achieved by the outgrowth of capillary buds from the fascia flap (recipient blood vessels) uniting with those on the adventitia (donor blood vessels) of the tracheal segment. Inosculation is the establishment of direct vascular anastomoses between the vascularized soft tissue flap and the adventitia of the trachea.

Compared to a free skin graft, there are two additional barriers to revascularization for a tracheal allograft. The cartilage rings and intercartilaginous ligaments may interfere with the revascularization of the mucosal lining of the cartilaginous trachea. Cartilaginous tissue does not allow for the ingrowth of blood vessels. Revascularization
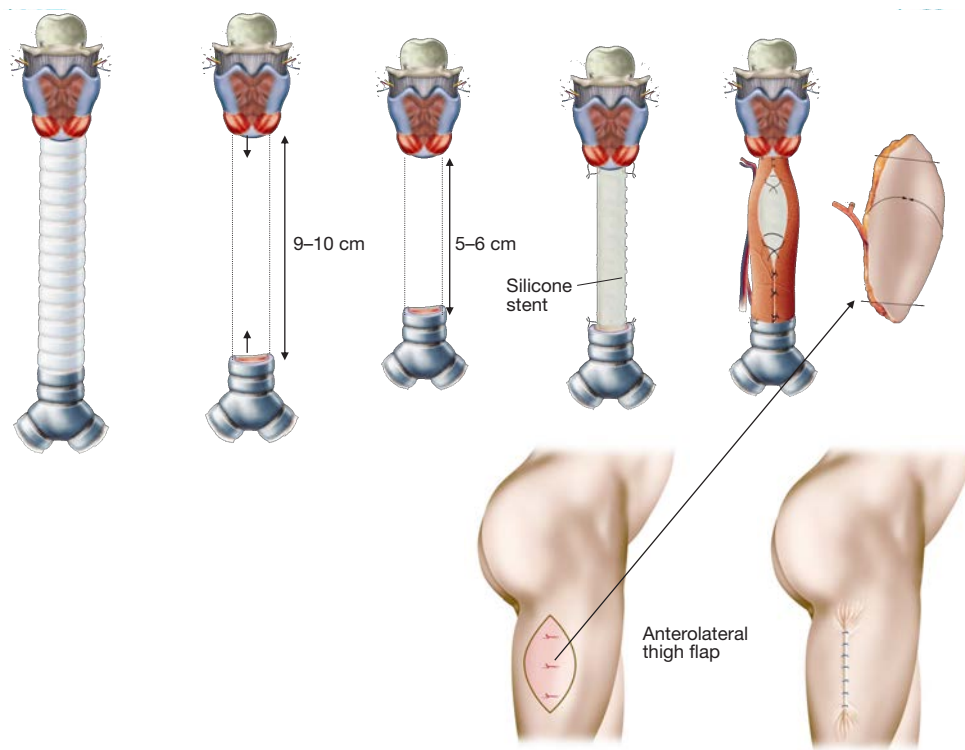
Figure 2 Palliative treatment of long-segment tracheal defects.
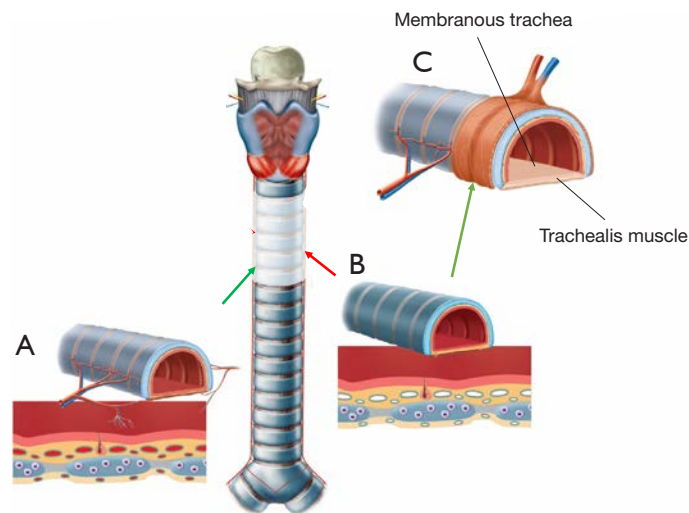

Figure 3 Vascularized and de-vascularized trachea. (A) In the healthy native trachea, the blood supply is ensured by a network of small blood vessels penetrating the trachea between the cartilage rings. Successful grafting (green-colored arrow) of a segment of the trachea requires the segment to have an intact and independent blood supply; (B) prelevation of a tracheal segment inevitably leads to interruption of its blood supply. Successful transplantation (red-colored arrow) requires restoration of an adequate blood supply, as in A. This is extremely difficult; (C) de-vascularized tracheal segments can become revascularized in a heterotopical position. The cartilaginous trachea can undergo progressive revascularization when wrapped with well-vascularized tissue. In humans, revascularization of the membranous trachea will be difficult because the trachealis muscle forms a barrier for mucosal revascularization. We learned that heterotopic tracheal revascularization occurs in a safer way after excision of the membranous trachea.
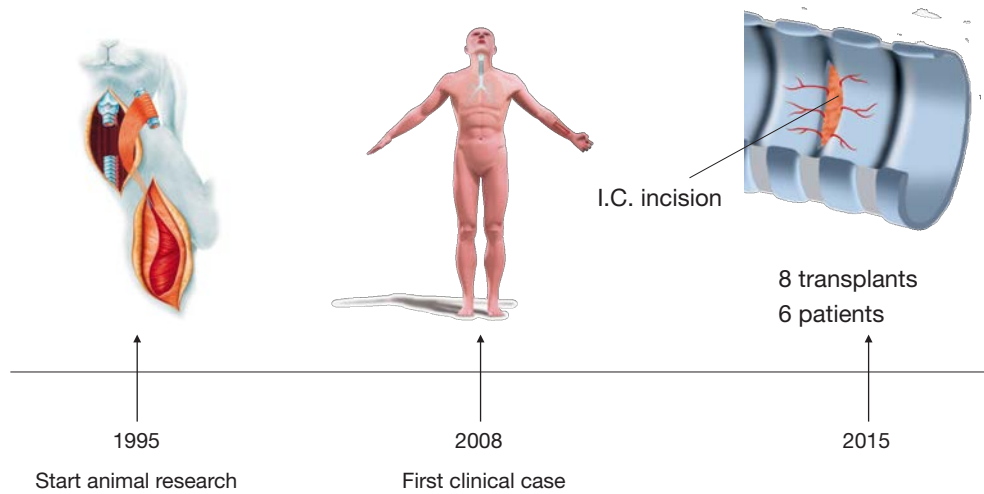
Figure 4 Overview of our experience in tracheal allotransplantation. Eight transplants were used in six patients. Two of the initial transplants were lost after withdrawal of immunosuppressive therapy. Important is to make partial incisions of the intercartilaginous (I.C.) ligaments at the time of forearm implantation to preserve the viability of the transplant after cessation of immunosuppressive drugs.
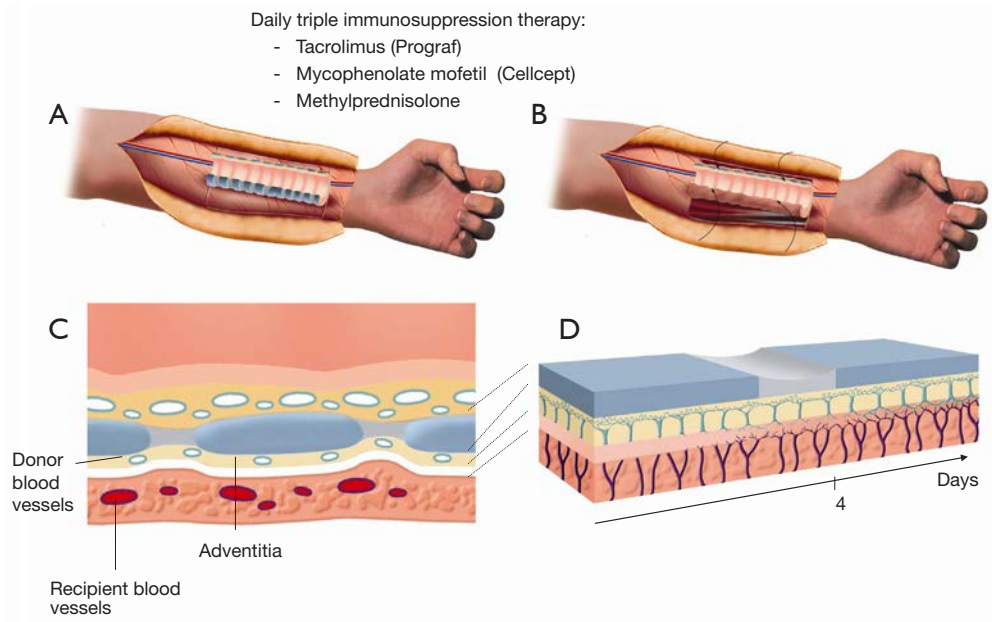
Figure 5 Orthotopic tracheal revascularization. The approach to heterotopic revascularization is shown. The forearm skin is incised and dissected away from the underlying fascia and subcutaneous tissue. After removal of the membranous part (A), the trachea is wrapped with the radial forearm fascia (B) and the forearm skin flaps are sutured to the incised trachea. Revascularization can be achieved by the outgrowth of capillary buds from the native vascularized tissue to unite with capillaries in the adventitia of the trachea (C). This link-up should be well advanced by the third day (D).
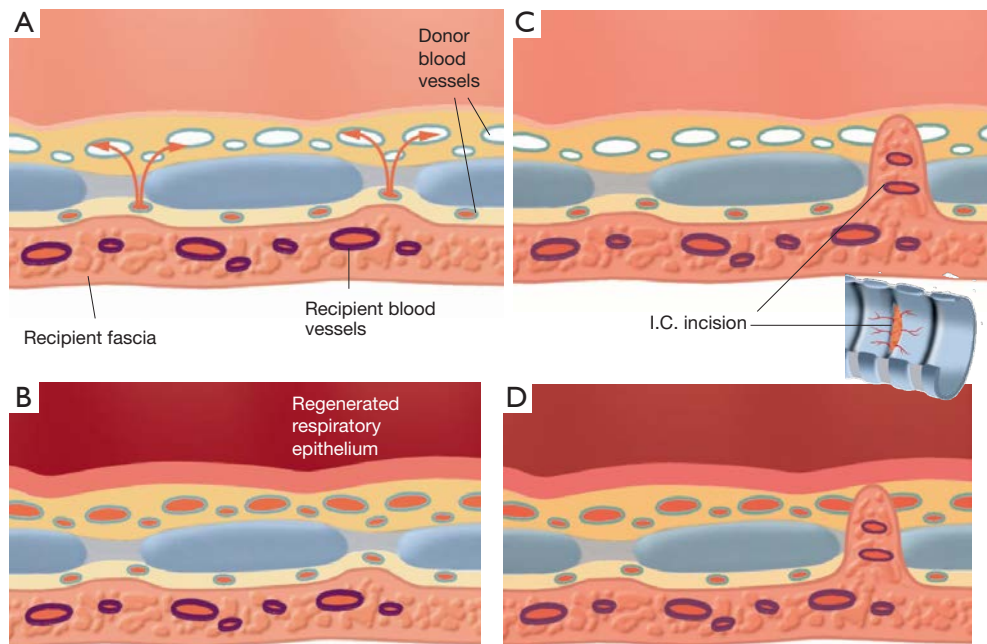
Figure 6 Tracheal revascularization and mucosal regeneration. (A) The cartilaginous trachea is revascularized (red arrows) by the surrounding tissues through the intercartilaginous ligament; (B) regeneration of the donor respiratory epithelium occurs simultaneously with the revascularization process; (C,D) partial incision of the intercartilaginous ligament (inset) will bring the recipient blood vessels closer to the donor submucosal capillaries, which will result in advancing of the revascularization process.

of the mucosal layer of an avascular tracheal segment occurs through the intercartilaginous ligaments (*Figure 6*). Full revascularization and mucosal regeneration of the cartilaginous trachea can be achieved within 2–4 months of the trachea being implanted in the forearm. Incision of the intercartilaginous ligaments will foster the revascularization process by bringing the recipient blood vessels closer to the submucosal capillaries.

A tracheal allotransplant is a composite tissue transplant that may be used to restore the airway, with the goal of improving quality of life. The benefits garnered by tracheal allotransplantation have to be balanced against the morbidity of long-term immunosuppression therapy. Immunosuppressive medication should be withdrawn before immunosuppressant-related complications occur. The cartilage tissue seems to escape immunologic rejection owing to the absence of blood vessels, and because the chondrocytes are protected within a matrix (6,8,9). In our initial patient series of tracheal transplantations, it became clear that the intercartilaginous ligaments formed an obstruction for the ingrowth of native blood vessels (*Figure 7*). The placement of intercartilaginous incisions at the time of forearm implantation was an important adaptation. The

incisions of the intercartilaginous ligaments facilitated revascularization, enabling the ingrowth of recipient vessels into the submucosal space of the transplant. When incisions through the intercartilaginous ligaments were made at regular intervals, full revascularization and mucosal regeneration of the cartilaginous allotransplant could be obtained in a shorter time period. Moreover, regularly spaced intercartilaginous incisions provide avenues for angiogenic recipient vessels to breach the ligamentous barrier and thus grow into the submucosal space of the transplant tissue after withdrawal of immunosuppressants.

Clinical examples

Of the six patients treated so far, five patients were treated for a long-segment stenosis and one patient was transplanted to resolve a long-segment laryngotracheal involvement by a chondrosarcoma. Our approach to a long-segment stenosis is shown in *Figure 8*.

Tracheal allotransplantation was used in the treatment of a patient with an extended laryngotracheal chondrosarcoma. The patient involved was a 63-year-old man. The tumor developed over a period of more than 10 years. His airway
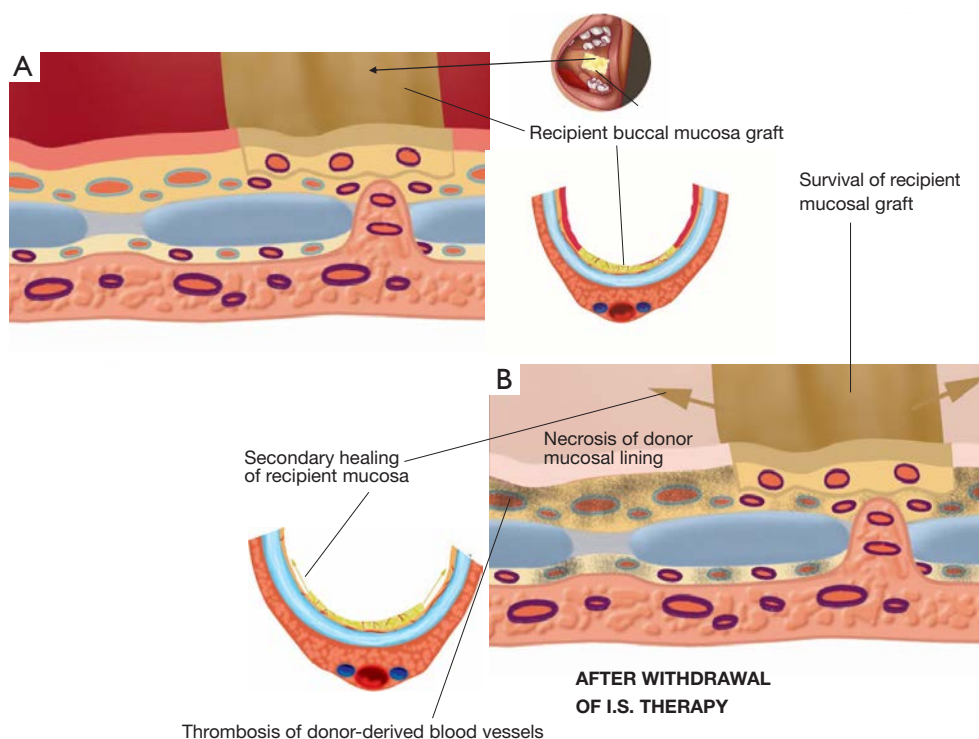
Figure 7 Importance of intercartilaginous incisions and of recipient mucosa. (A) After tracheal allograft revascularization and mucosal regeneration, recipient buccal mucosa can be introduced into the midportion of the allotransplant. A mucosal defect is created in the central part of the transplant and the midportion is grafted with a full-thickness mucosal graft from the recipient's buccal area; (B) after withdrawal of immunosuppressive drugs: immunologically-induced lymphocytes attack the microcirculation. Inflammatory vascular infiltrates will lead to thrombosis of donor-derived blood vessels and to necrosis of the mucosal layer. The intercartilaginous ligaments were observed to be acting as a barrier to the ingrowth of recipient blood vessels. The intercartilaginous incisions will allow for ingrowth of recipient blood vessels into the submucosal space of the transplant. These newly formed recipient blood vessels will allow the recipient mucosal lining in the midportion of the transplant to survive immunosuppressant withdrawal. The surviving recipient mucosal graft will allow for secondary healing of the areas of donor epithelial lining that underwent necrosis (yellow arrows).

could be preserved by the placement of a silicone stent. Due to the stagnation of secretions, he required periodical bronchoscopic cleaning of the stent. Since the last time, he had developed several acute episodes of stent blockages, which made definitive treatment necessary. Four months after implantation of a suitable allograft in the left forearm, the tumor was resected through an anterior cervical incision with a sternotomy extension (*Figure 9*). The potential for tumor progression while under immunosuppression for a low-grade malignancy was considered to be low and was confirmed by CT scan at the time of orthotopic transplantation, which demonstrated a nearly unchanged tumor bulk. Immunosuppressive medication was gradually phased out between 15 and 18 months after orthotopic transplantation. The transplant's morphology remained

intact after withdrawal of immunosuppressive therapy. It seems that the mucosal repopulation of the transplant after cessation of immunosuppressants can occur with minimal loss of airway lumen (*Figure 10*).

A circumferential airway repair may be necessary after resection of malignant tumors. Tracheal allotransplantation at the time of tumor resection will be possible only for low-grade malignancies and not for other malignant tumors, because of the risk of tumor progression in the 3-month period of pretransplant immunosuppression. A circumferential defect left by tumor resection can be reconstructed temporarily with a stent wrapped in vascularized tissue. This type of reconstruction must be considered temporary due to inevitable stent-related complications. Tracheal allotransplantation may be considered in those patients with a temporary repair who
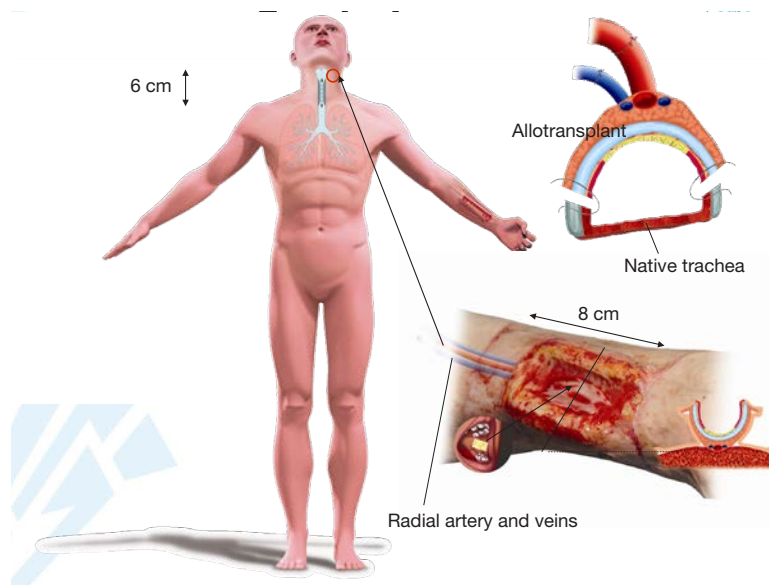
Figure 8 Allotransplantation of a long-segment tracheal stenosis. Orthotopic transplantation of a tracheal transplant to resolve a long-segment (6 cm) airway stenosis is illustrated. An eight cm long tracheal allotransplant is implanted at the forearm. During the first weeks the luminal site of the transplant is protected by the application of fibrin glue. After revascularization, a buccal mucosa graft from the recipient can be applied to the midportion of the transplant to allow for a safe withdrawal of immunosuppressive drugs. The long-segment tracheal stenosis is incised longitudinally (double arrow). After full revascularization and mucosal regeneration have been achieved, the tracheal allotransplant is transplanted from the forearm to the airway defect on a radial vascular pedicle. The radial blood vessels are sutured to the neck vessels to facilitate revascularization. The cartilaginous trachea is sutured into the airway defect to restore the concavity of the airway lumen. Withdrawal of immunosuppressive therapy can start 1 year after orthotopic transplantation.
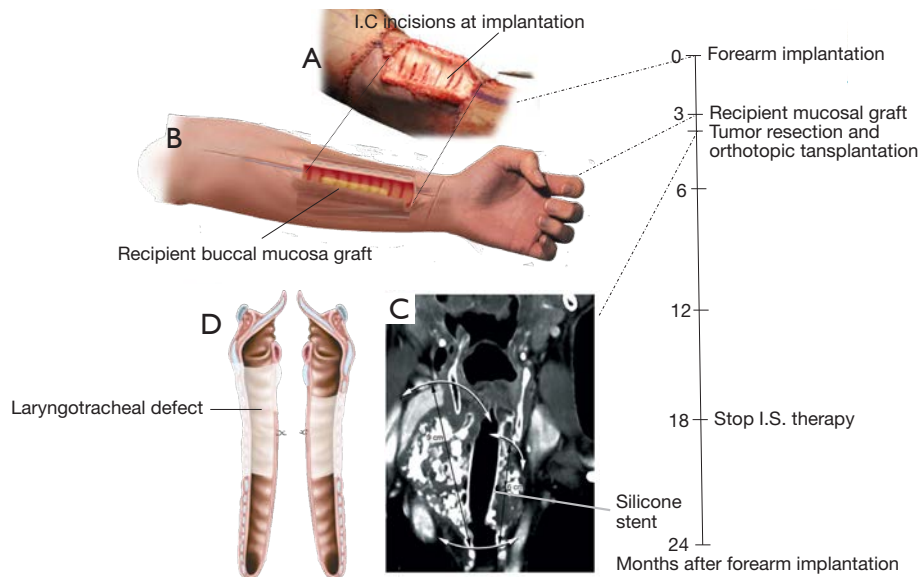
Figure 9 Patient with low-grade chondrosarcoma. Tracheal allotransplant at time of forearm implantation with I.C. incision (A) and after full revascularization with a recipient buccal mucosa graft at it's midportion (B). Tumor involvement visible on a coronal CT scan image (C). The airway lumen is bridged by a silicone stent. The degree of resection is indicated with white, two-headed arrows. The lengths of the tracheal resection were 9 cm (right) and 6 cm (left) (scale =1 cm). After 4 months, the tumor could be resected and the tracheal allotransplant was used to repair the laryngotracheal defect (D).
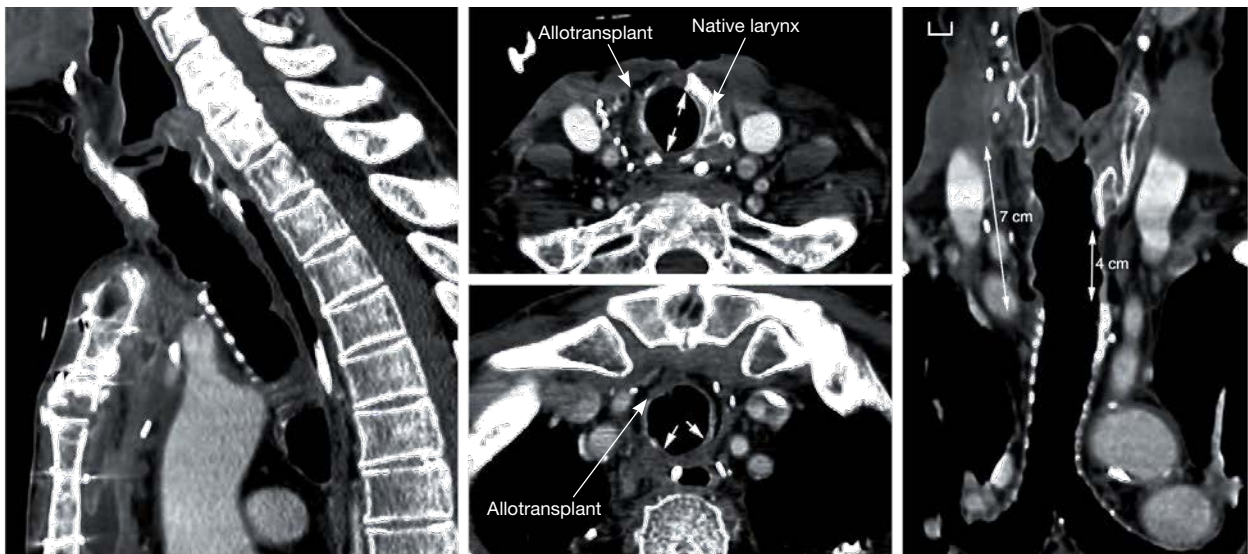
Figure 10 CT scan after orthotopic transplantation and after withdrawal of immunosuppressive drugs. A CT scan 2 years after orthotopic transplantation and 6 months after cessation of all immunosuppressive therapy is shown. Note the absence of cartilage calcification in the allotransplant (scale =1 cm). (A) Sagittal reformatted CT scan; (B) axial CT scan at laryngeal level; (C) axial CT scan at level of cervical trachea; (D) coronal reformatted CT scan.
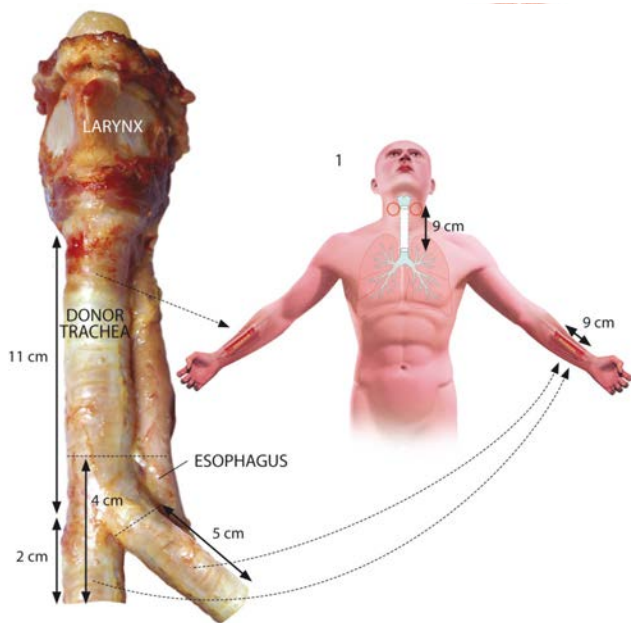

Figure 11 Implantation of two tracheal allografts for circumferential airway repair. The full length of the trachea and main bronchi can be used for allotransplantation. Two cartilaginous tracheal segments with a length of 9 cm may be implanted at two forearm sites. By suturing the two allotransplants together, a tube may be created for circumferential airway repair.

remain tumor-free.

The best protocol for circumferential allotransplantation may lie in a bilateral transplantation of the cartilaginous trachea (*Figures 11,12*).

Tracheal regeneration

Regeneration versus secondary healing

The relative contribution of tissue regeneration versus scarring in the healing of the airway mucosal lining depends on the extent of injury inflicted. A superficial epithelial wound can heal by way of regeneration of the surface epithelium (*Figure 13*) (10). Indeed tissues with a high proliferative capacity, such as airway tract epithelia, renew themselves continuously and, after injury, can regenerate above the basal membrane as long as the stem cells in these tissues have not been destroyed.

If a tissue injury is severe and involves damage of both epithelial cells and the submucosal layer, healing cannot be accomplished by regeneration alone. Under these conditions, the main healing process is repair by deposition of collagen, causing the formation of a scar. Future therapies should aim to promote regeneration and reduce scar tissue formation when dealing with full-

thickness mucosal tracheal defects. Exploration of the potential use of stem cells for true regenerative healing is ongoing. The present challenge for regenerative medicine is to overcome the barriers to regeneration of the mucosal and epithelial lining in full-thickness epithelial defects. However, regeneration of full-thickness mucosal defects is not yet possible.
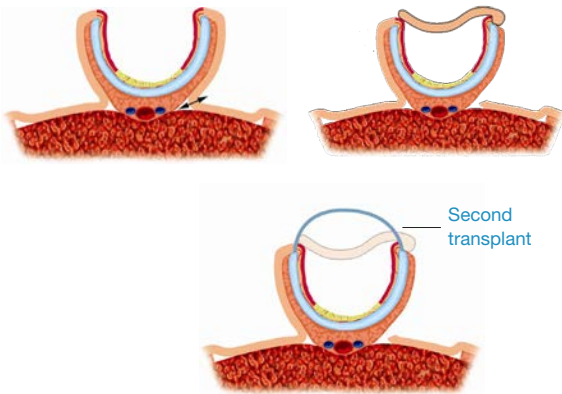

Figure 12 Circumferential airway repair. The first transplant is used to restore the posterior and lateral walls of the airway. A part of the forearm skin can be included as a temporary reconstruction of the anterior wall. In a second operation, the second transplant can be used to replace the forearm skin and to further augment the airway lumen.

The unrealistic prospect of tracheal regeneration

Since 2008 the trachea has been termed the first human organ that can be man-made with stem cells (11). Meanwhile an engineered trachea has been implanted in several patients. This achievement has received a lot of attention in medical journals as well as in the press. Indeed, the engineered windpipe was seen to be the first step towards other forms of organ regeneration. Classic organ transplantations with their typical side effects due to anti-rejection medication could then be replaced by growing organs from the body's own cells. However, the optimism surrounding organ regeneration has proved to be completely unfounded. In fact, the engineered trachea is an example of blatant scientific deception.

The engineered trachea was represented as a regenerated trachea after applying bone marrow cells to a de-cellularized (12) or synthetic scaffold (*Figure 14*) (13). There is no scientific foundation whatsoever to assume why stem cells would support airway tissue regeneration in this setting. In addition, even if a trachea-like organ would be generated, it would irrefutably fail after implantation if adequate blood supply had not been restored. As expected, the implantation of de-cellularized and synthetic scaffolds resulted in extremely high morbidity and mortality rates (14). At this point in time, this form of airway regeneration should be regarded as hypothetical and scientifically unfounded (15,16).
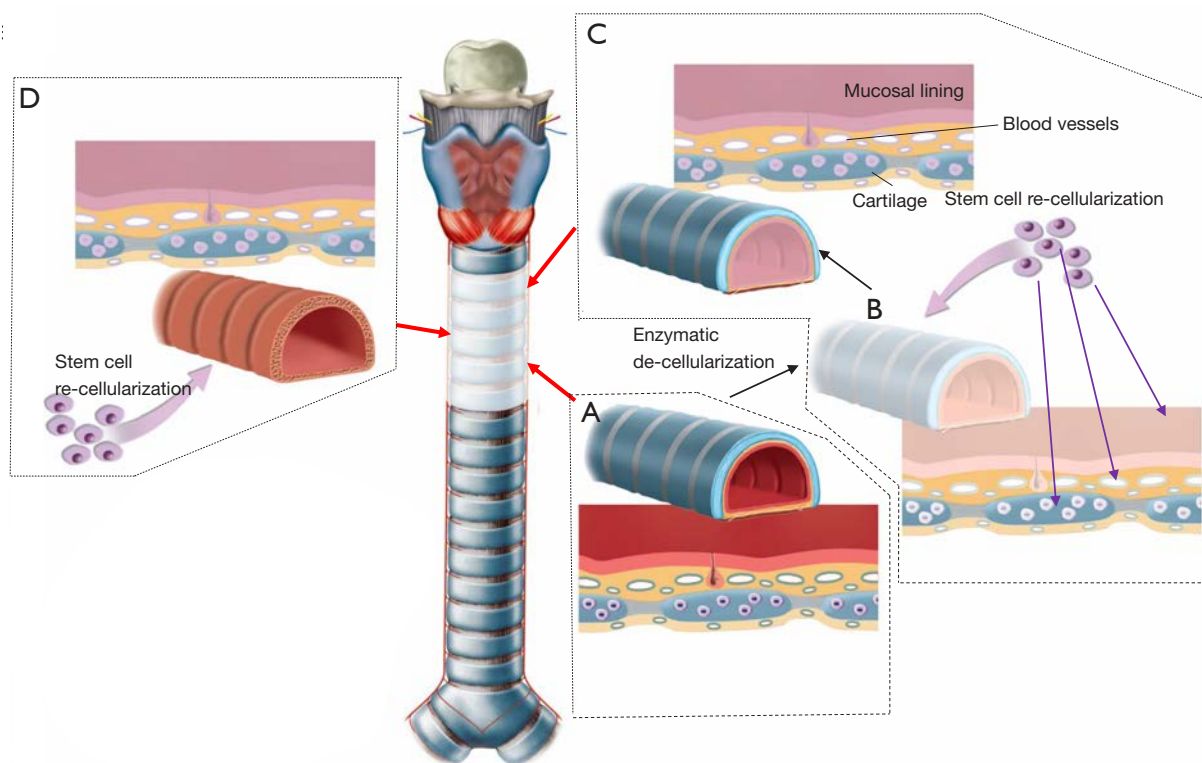

Figure 13 Regeneration of airway tissue. The basement membrane of the mucosal layer supports a pseudostratified epithelium, the surface layer of which is columnar and ciliated, with deeper layers of oval or rounded basal cells. A superficial epithelial wound can heal through regeneration of the surface epithelium. Tissues with high proliferative capacity renew themselves continuously and can regenerate after injury above the basal membrane through proliferation and differentiation of basal cells.

Figure 14 How the engineered trachea was represented. (A) De-vascularized native trachea; (B) as a first step towards a presumed 'stem-cell engineered regenerated trachea', a detergent is used to destroy all viable cells, leaving a scaffold of connective tissue; (C) a 'stem-cell engineered regenerated trachea': it is hypothesized that stem cells penetrate the connective tissue and subsequently regenerate cartilage, blood vessels and respiratory mucosa. This presumed regenerated trachea is implanted without restoration of any blood supply (red-colored arrow); (D) it is hypothesized that stem cell-mediated re-cellularization of a synthetic scaffold may also lead to a fully regenerated trachea that can be transplanted inside the airway (red-colored arrow).

Acknowledgements

None.

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Tracheal suspension by using 3-dimensional printed personalized scaffold in a patient with tracheomalacia

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Abstract: The major methods are used to fix or stabilize the central airways and major bronchi with either anterior suspension and/or posterior fixation for severe tracheomalacia (TM). Many support biomaterials, like mesh and sternal plate, can be used in the surgery. But there are no specialized biomaterials for TM which must be casually fabricated by the doctors in operation. Three dimensional printing (3DP) has currently untapped potential to provide custom, protean devices for challenging and life-threatening disease processes. After meticulous design, we created a polycaprolactone (PCL) scaffold for a female patient with TM, which would support for at least 24 months, to maintain the native lumen size of collapsed airways. Using 4-0 Polyglactin sutures, we grasped and suspended the malacic trachea into the scaffold. A remarkable improvement can be observed in the view of bronchoscope and chest CT after surgery. In the narrowest cavity of malacic trachea, the inner diameter increased from 0.3 to 1.0 cm, and the cross sectional area increased 4–5 times. The patient felt an obvious relief of dyspnea after surgery. In a word, the 3DP PCL scaffold can supply a personalized tool for suspending the malacic trachea in the future.

Keywords: Tracheomalacia (TM); three dimensional printing (3DP); polycaprolactone scaffold; 4D materials; suspension

Introduction

Tracheomalacia (TM) is a condition of excessive collapse of the airway during respiration that can lead to life-threatening cardiopulmonary arrests (1,2). The congenital TM is often associated with tracheoesophageal fistula/esophageal atresia, bronchopulmonary dysplasia, and prematurity. Secondary TM occurs from external compression by vascular structures, tumors or cysts, or internal pressure caused by prolonged endotracheal intubation or tracheostomy (3). Mild and moderate TM tends to resolve over time with

growth and development of a child patient (4,5). Severe cases need to be addressed because of significant morbidity and mortality (3).

Current therapies for severe TM include tracheostomy tube placement with prolonged mechanical ventilation, cardiovascular procedures to relieve compression from abnormal anatomy, and intraluminal airway stents. However, all these therapies have their instinct weakness, and the severe TM is lacking in an adequate intervention (6). Tracheostomy tube placement always accompanies tube occlusion with an incidence of 43%, which may cause

respiratory arrest, especially for child patient (7). Aortopexy is the most common method for treatment of severe TM. However, it carries a high complication rate, including pericardial effusion, mediastinitis, and recurrence or regression of disease with cardiopulmonary arrest (8). Tracheal stenting can be performed without serious invasion, but migration of stenting and the recurrence of airway obstruction due to granulation tissue formation are another problem that can not be ignored (8).

Furthermore, the external tracheal stabilization techniques were attempted. Some experiments proved that the animals with external splinting were free from signs of respiratory distress post-operatively and no serious complication was found (9). However, the fixed-size external implants may restrict growth of trachea and inhibit natural improvement of the disease, and the premature splint degradation and loss of airway support are also the serious problems (9). Three-dimensional printing (3DP) arose from the automotive and aerospace industry in the 1980s and has subsequently been applied to customization of medical devices (10). 3DP has currently untapped potential to provide custom, protean devices for challenging and life-threatening disease processes. After meticulous design, we created a bioabsorbable external scaffold, which would support for at least 24 months, to maintain the native lumen size of collapsed airways. It allows transverse plane movement and normal cervical range of motion, but does not alter the mucociliary architecture of airway. After being placed extralumenally, the symptoms of the patient were improved remarkably, and there was no any complication.

Operative techniques

Characteristics of the patient

A 46-year-old female patient with tracheostenosis was referred to our department for treatment. The patient was diagnosed with endobronchial tuberculosis 2 years ago, and she received a regular antituberculosis therapy by taking isoniazid, rifampin, pyrazinamide and ethambutol. During the treatment, the patient suffered from dyspnea, and this symptom has developed gradually. The bronchoscope and chest computed tomography (CT) was subsequently performed, which showed a length of malacia in the trachea. Considering the development of the disease, a follow-up by using bronchoscope and chest CT was made every 3–6 months in the last 2 years, and the biopsy of trachea mucosa was also performed to detect the mycobacterium

tuberculosis. Until no advancement of tracheomalacia had been found for 6 months, the further surgery was prepared.

Production of trachea scaffold

The scaffold was designed and made by Xi'an Jiaotong University. All of the parameters were set according to the CT value of tracheal malacic segment. As shown in the *Figure 1A,B*, the length (L) and external diameter (D) was 70 and 22 mm respectively. Moreover, the structure of the scaffold was projected as thread type with a pitch of 2 mm (d) and an open ring of 270°. For satisfying the biocompatibility and intensity, we selected the polycaprolactone [PCL, $(C_6H_{10}O_2)_n$] as the raw material of scaffold. The PCL was purchased from Daigang Biomaterial Co., Ltd (Jinan, China). The molecular weight was 80,000 units, and the intrinsic viscosity number was 0.5–1.0 dL/g. In theory, PCL with the molecular weight above 65,000 can stably exist 2 years *in vivo*, and then it will gradually degrade into H_2O and CO_2 (11). Since the acid environment after degradation can stimulate the hyperplasia and fibrosis of surrounding tissues, the malacic trachea can solidify gradually. The melting point was 58–64 ℃. The 3DP technique of fused deposition modeling was applied with the melting temperature of 80 ℃. Otherwise, we utilized 3DP polylactic acid tracheal model to evaluate the operative status of the malacic segment. Due to originating from the DICOM style file of thoracic CT, the 3DP model mimicked the malacic trachea. The products were showed in *Figure 1C,D*.

Surgical procedure

The tracheal malacic segment was assessed by chest CT and bronchoscope before (*Figure 2A,B*) and after (*Figure 2C,D*) the surgery. In the field of bronchoscope, the tracheal wall of malacic segment collapsed, especially in expiratory phase (*Figure 2A*). And the inner diameter of the narrowest cavity was only 0.3 cm. The three-dimensional reconstruction of CT images showed the tracheal malacic segment, which was about 1.5 cm above the carina of trachea (*Figure 2B*). The length of malacic segment was 6 cm, while the length of entire trachea was 11.5 cm. Thus, it is difficult for directly resection of the malacic segment and end to end tracheal anastomosis. After being evaluated by an experienced team completely, the suspension surgery was performed. The patient was intubated in the supine position, and then she was reversed in left lateral horizontal position and had a posterolateral thoracotomy in the fourth intercostal space.
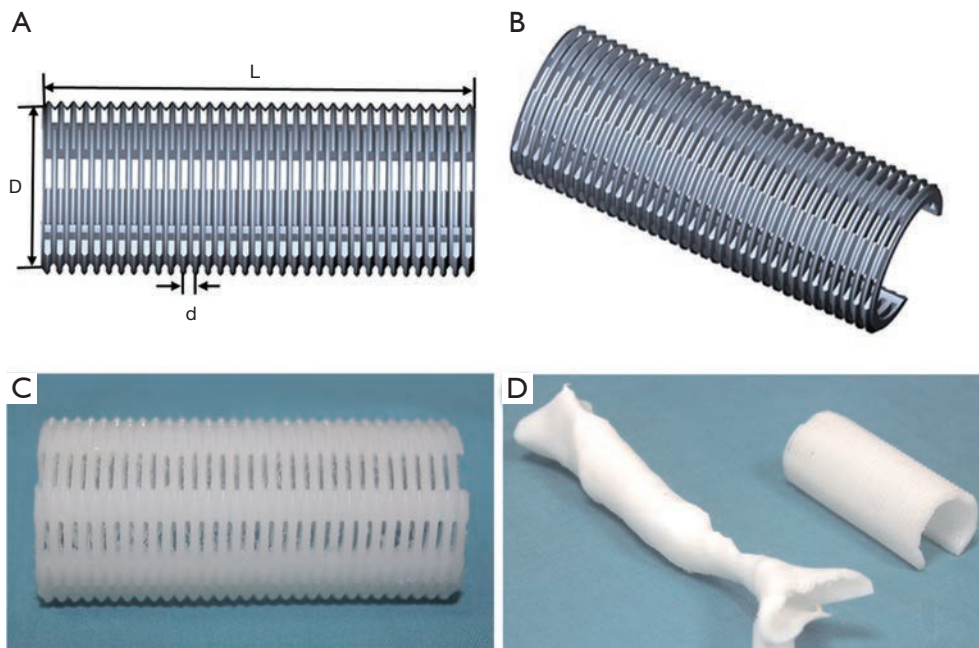
Figure 1 The schematic diagram and product of the 3DP scaffold. L =70 mm, D =22 mm, d =2 mm. 3DP, three dimensional printing.
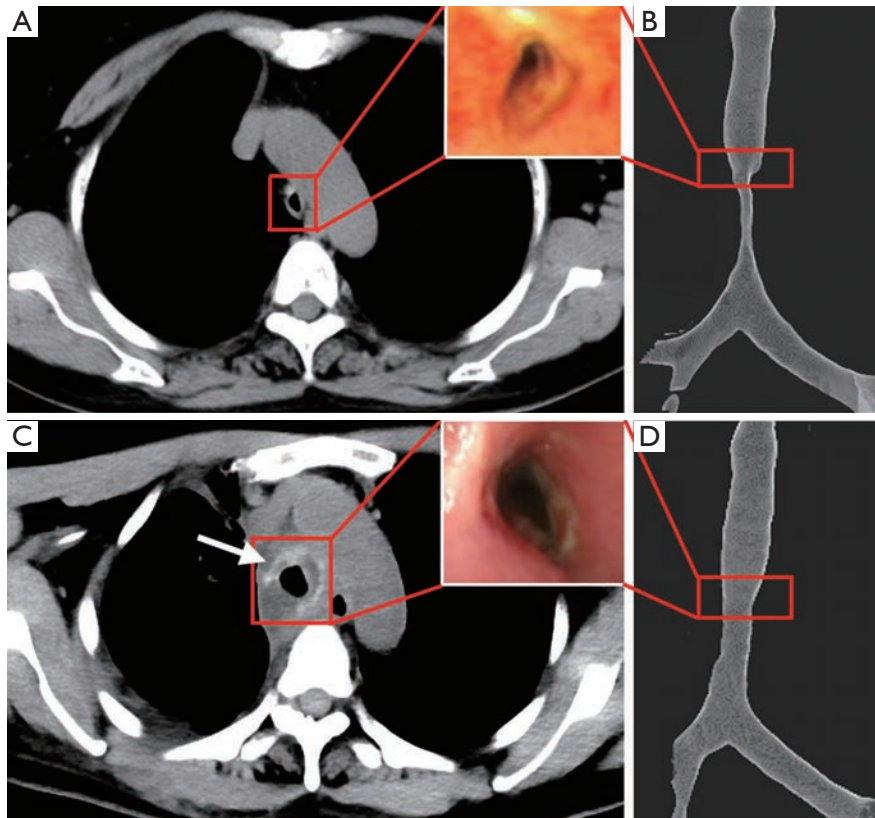

Figure 2 The images of bronchoscope and tracheal CT before (A,B) and after (C,D) the suspension surgery. The red frame draw out the images in the same cross-section, and the white arrow pointed out the image of scaffold *in vivo*.
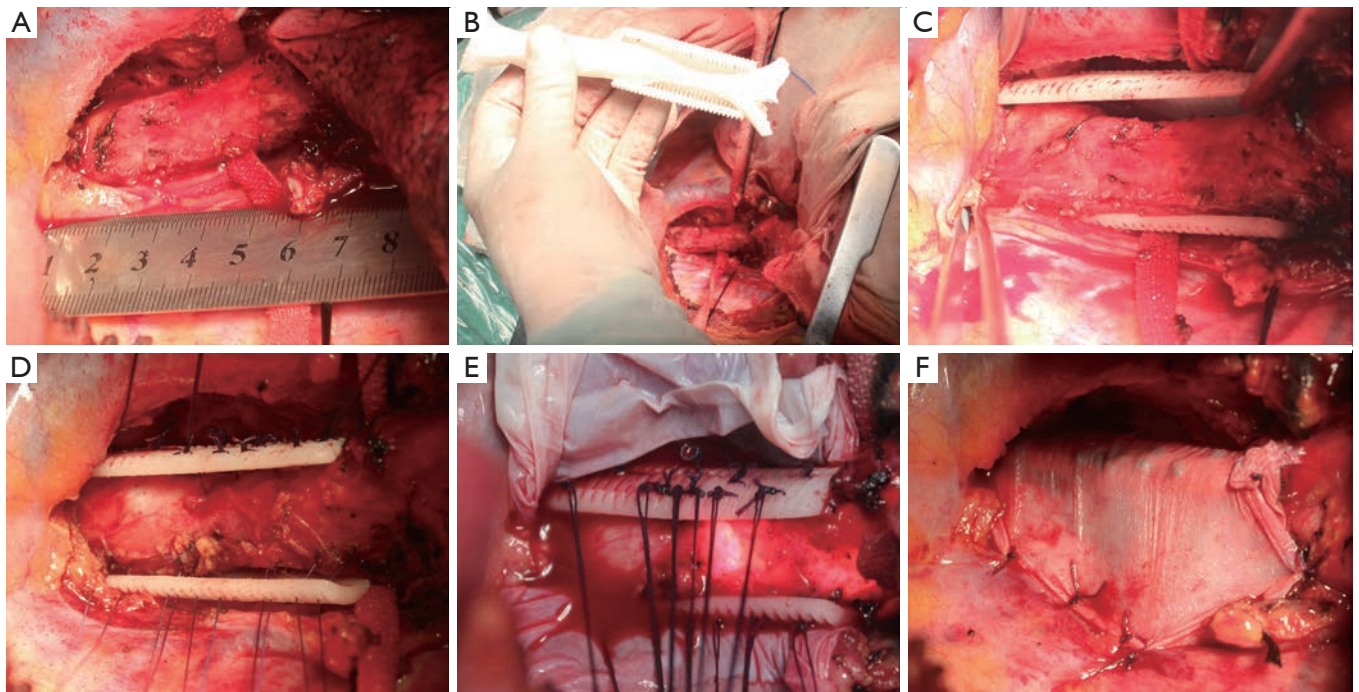
Figure 3 The surgical procedures of entire suspension. (A) The malacic trachea was split from other organs; (B) the malacic segment was measured and compared with the 3DP tracheal model in surgery; (C) the 3DP scaffold was placed around the malacic trachea; (D) the malacic trachea was suspended under observation of bronchoscope; (E) the contiguous suspension positions in an axial direction were 0.5–1.0 cm apart; (F) an artificial pleural patch was put around the 3DP scaffold to alleviate the abrasion to other organs. 3DP, three dimensional printing.

As shown in *Figure 3A*, the malacic trachea was split from other organs. The azygos vein was ligatured and cut because of the obstruction to malacic segment. Furthermore, the malacic segment was measured and compared with the 3DP tracheal model in surgery (*Figure 3B*). It can be clearly demonstrated that 3DP tracheal model is accurately matched with the actual malacic trachea. Then, the 3DP scaffold was placed around the malacic trachea (*Figure 3C*). Besides the complete separation of malacic trachea, the cooperation of anesthetist was the most important matter in the entire procedure. Because the intubation tube can not pass through the narrowest cavity, any operation in the malacic segment may result in the acute anoxia. The ventilatory pressure and capacity must be increased properly to maintain the oxygen saturation. Using 4-0 Polyglactin (Ethicon, Somerville, USA) sutures, we grasped and suspended the malacic trachea while bronchoscope was simultaneously performed to define and choose optimal points for suture placement precisely (*Figure 3D*). The sutures can be tied to the holes of scaffold, and at least four

uniform positions were suspended in a cross section of malacic segment. The contiguous suspension positions in an axial direction were 0.5–1.0 cm apart (*Figure 3E*). At last, we put an artificial pleural patch around the 3DP scaffold to alleviate the abrasion to other organs, such as esophagus and precava (*Figure 3F*). After the accomplishment of whole surgery, the intubation tube with 6.5 mm passed through the malacic segment.

The patient was transferred into the intensive care unit after surgery, and she received assisted mechanical ventilator for 48 hours. In the first 24 hours, the intubation tube was put in the malacic segment to support the tracheal wall. And then we pulled out the tube above the malacic segment in the next 24 hours. After recovering autonomous respiration, the patient was extubated. The patient felt an obvious relief of dyspnea after surgery. She discharged from the hospital in 2 weeks after surgery. A detailed assessment about the efficacy and adverse reaction was performed. In *Figure 2C,D*, a remarkable improvement can be observed in the view of bronchoscope and chest CT. In the narrowest cavity of

malacic trachea, the inner diameter increased from 0.3 to 1.0 cm, and the cross sectional area increased 4–5 times. In the chest CT, the scaffold can be clearly viewed (the white arrow in *Figure 2C*). In the follow-up of first 3 months, the patient had a remarkable improvement of breathing and physical strength. The chest CT images showed the scaffold was stable in the mediastinum, and the cavity of malacic trachea was the same as that in *Figure 2C*. No adverse reaction and toxicity were observed in the follow up.

Discussion

Many diseases, such as mediastinal lesion, tuberculosis, and other congenital factors, could compromise the blood and nutrient flow to the supporting cartilage, with the result of softening and collapse of the trachea wall (1-3). Anterior TM always occurs due to malformed tracheal cartilage, while posterior TM resulted from the membranous component. Currently there is no consensus regarding radiographic evaluation, standardized endoscopic evaluation, surgical approach, and medical treatments for TM (6). Multiple techniques have been created for the treatment of TM, however, there is currently no evidence supporting one therapy over another (6). The majority of methods are used to fix or stabilize the central airways and major bronchi, such as direct tracheobronchopexy, with either anterior suspension and/or posterior fixation for severe TM (12). The most common anterior tracheobronchopexy is aortopexy. Yet, a recent meta-analysis of aortopexy reported an overall complication rate of 15% and a mortality of 6%, even 4% of patients with worsening symptoms (13). This study suggested that there was room for improvement of tracheobronchopexy.

Many support biomaterials like mesh and sternal plate can be used to fix or stabilize the anterior cartilaginous or posterior membranous components (14). There are no specialized biomaterials for TM which must be casually fabricated by the doctors in operation. Thus, the support biomaterials with personalized design, good biocompatibility and sufficient mechanical strength should be developed for the tracheobronchopexy. In 2013, Zopf *et al.* (15) firstly created a 3DP scaffold to suspend the malformed bronchus. It must be worth noting that this PCL scaffold can not only satisfy the most requirements of tracheobronchopexy, but also biodegrade with the passage of time. This "4D materials" can make benefit to the child patient in growth period. In the following study of this group (16), another two patients with

tracheobronchomalacia consecutively received bronchopexy by using the 3DP PCL scaffold. It has been proved the treatment efficacy, adverse reaction and biodegradation in the follow-up period. 3DP technique provided a novel tool to fabricate a personalized tracheal scaffold. We have used 3DP technique to make titanium sternum and ribs for reconstruction of chest wall previously (17). Furthermore, we continued to use the fused deposition modeling to make the PCL scaffold. The main lesion of TM was about 6 cm in the patient's trachea which has reached the limitation of tracheal resection. And the primary endobronchial tuberculosis also prevented the traditional resection. After efficient treatment for endobronchial tuberculosis in 2 years, the suspension for malacic trachea was the optimal option. We designed the 3DP tracheal model and scaffold according to the tracheal CT images, which can make certain of the accuracy and matched-degree. As compared with the conventional materials, 3DP PCL scaffold can fix both the anterior and posterior tracheal wall. Meanwhile, the sufficient elasticity and intensity can support the compression from surrounding organs.

In a word, the 3DP PCL scaffold can supply a novel tool for suspending the malformed bronchus. But there are still some limitations that need to be addressed. Firstly, there is only one case in this research. The feasibility and safety of the scaffold must be proved in more samples. We made our best to select the uniform position to suspend the malacic trachea, but some triangles in a cross section were also observed. Maybe the structure of open ring is the main reason, and the surgical skills should be further improved. Moreover, more performance parameters, including materials, processing technic and structure design, must be discussed and confirmed for patients at different ages. Otherwise, it must be worth noting that the 3DP technique is difficult to be approved by FDA and CFDA. Because the 3DP product is individual and personalized for the specific patient, it is difficult to quantify and batch. This is also the common characteristic that all 3DP products must face.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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New developments towards the management of severe cases of tracheobronchomalacia

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Comment on: Huang L, Wang L, He J, *et al*. Tracheal suspension by using 3-dimensional printed personalized scaffold in a patient with tracheomalacia. J Thorac Dis 2016;8:3323-8.

Tracheobronchomalacia is a severe anomaly that can lead to acute life-threatening events, due to collapse of the upper airways (1). The congenital form is the most frequent occurring, usually in conjunction with esophageal atresia (2), but sometimes acquired tracheobronchomalacia may occur as described by Huang *et al.* (3).

Tracheobronchomalacia knows a spectrum of symptomatology, varying from a typical cough due to the vibration of the tracheal wall, to complete collapse of the tracheobronchial airways (4). Depending on the extension of the anomaly artificial ventilation with high post-expiratory pressures (PEEP) may be necessary to keep the airways open. Many of these patients may need a tracheostomy (5) to maintain a sufficient open airway, but particularly if the malacia extends into the bronchi a simple tracheostomy may not suffice. There are a number of surgical options, of which the aortopexy is the most frequently used technique (2). The aortic arch and trachea are bound by connective tissue. By lifting the aortic arch against the backside of the sternum the anterior wall of the trachea is also lifted, preventing the insufficient tracheal rings from collapsing. This technique is nowadays also possible by thoracoscopy, reducing the trauma from major thoracotomies (6). Recurrence rate varies up to 35% (7).

If the major problem is not the insufficient tracheal rings but instead a floppy pars membranacea on the posterior side, (thoracoscopic) posterior tracheopexy against the prevertebral fascia is a good alternative (4). In normal children the pars membranacea forms 1/3 of the posterior wall of the trachea. In many neonates with esophageal atresia and tracheomalacia the pars membranacea extends over approximately half of the posterior wall and on expiration can easily close off the trachea, causing air entrapment and acute respiratory failure. Sometimes a combination of both is present, requiring both a posterior tracheopexy and an aortopexy (4).

However, mainly tracheal insufficiency can be dealt with in this way. If the anomaly extends further into the bronchi alternative measures will be necessary. There have been several attempts with intraluminal stents (8), but they have the tendency to dislodge or get obstructed, causing acute respiratory distress (9). There have also been attempts with external splinting (10). However as the child grows the splint will lose its function with recurrence of symptoms. Also at some time the splint needs to be removed again.

More recently with development of biodegradable scaffolds it is becoming possible to implant splints that will dissolve in time (11). In acquired tracheomalacia this may help to overcome the time necessary to have the defect be replaced by scar tissue (3). Based on CT-scan and or MRI a 3-D scaffold can be made to be placed externally onto the trachea keeping the trachea open and allowing for sufficient ventilation. In children this is not enough, because the child is growing. The group from Green in Michigan (7) developed a 4-D scaffold which can increase its diameter in time as the child grows, allowing for maintaining an adequate ventilation.

Although this may all seem very exciting there are some downsides as well. The indication for biodegradable scaffolds is very low, both in children and adults (7).

From an economic point this makes the production of biodegradable scaffolds less attractive. These 3-D or 4-D scaffolds will have to be "handmade" each time, which carry the risk of safety- and quality-issues. The United States Food and Drug Administration therefore is reluctant to allow the clinical use (7). To set up a clinical trial a minimum number of participants is necessary and that may be difficult to achieve. A non-interventional control group is not ethical due to the severity of the anomaly. It will need international collaborative studies to gain better insight in the ultimate outcome of this patient group.

Meanwhile other new exiting developments are progressing: nowadays biodegradable scaffold can be seeded with stem cells of different origin to allow tissue ingrowth (12). Multilayer scaffolds will allow better diffusion of nutrients and oxygen to allow the development of more complex structures or even organs in the near future (13,14). Custom designed integrated tissue and organ printing (ITOP) systems are being developed that can deposit 2–50 μm cell-laden hydrogels together with biodegradable polymers (12). With the use of CT or MRI data accurate tissue constructs can be made (13). Transferring these models into production of human tissue will be a next step to come.

Acknowledgements

Footnote

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Personalized interventions for tracheobronchomalacia

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Comment on: Huang L, Wang L, He J, *et al*. Tracheal suspension by using 3-dimensional printed personalized scaffold in a patient with tracheomalacia. J Thorac Dis 2016;8:3323-8.

There are several bronchoscopic, thoracoscopic and open techniques for the treatment of severe tracheobronchomalacia (TBM). The publication by Huang *et al*. in this issue of the journal focuses on a novel modality as a step forward towards a more personalized therapy. It is necessary to be aware of the two types of expiratory central airway collapse (ECAC) defined as excessive airway collapse during expiration. It is either a result of cartilaginous weakening (TBM) or redundancy and inward bulging of the posterior membrane [excessive dynamic airway collapse (EDAC)] (1) (*Figure 1*).

Both EDAC and TBM are characterized by excessive narrowing of the airway lumen during exhalation, which leads to the reduction of the cross-sectional area (CSA) as seen on paired inspiratory-dynamic expiratory computed tomography or bronchoscopy (1). Patients with ECAC have impaired quality of life (QOL). For example, in a cohort of patients with COPD, asthma and chronic bronchitis, the prevalence of ECAC was 5% and was associated with worse respiratory QOL as measured by St. George Respiratory Questionnaire (SGRQ) (2). It remains unclear what degree of airway collapse is pathologic, especially for EDAC. Distinguishing TBM from EDAC becomes clinically relevant since there is no clear role for stent insertion or surgical interventions in EDAC (3).

Tracheomalacia (TM), characterized solely by the weakness of tracheal cartilaginous wall, is not a common entity and is usually due to either chronic compression from tumors, vascular structures or caused by inflammatory processes involving the airway cartilage. It can be diffuse [as seen in Ehlers-Danlos syndrome or Relapsing Polychondritis (RP)] or localized (cartilaginous injury post tuberculosis, radiation or post-tracheostomy/intubation) (4). Treatments for patients with malacia depend on the etiology, severity of symptoms, degree and extent of airway collapse. Non-invasive positive pressure ventilation (NIPPV) can be offered to patients who are not severely impaired and who do not have severe, complete collapse of the cartilaginous wall. NIPPV has been successfully applied in patients with RP (5).

For more symptomatic patients with severe malacia not responding to the treatment of the underlying disorder and NIPPV, open surgery or bronchoscopic stent insertion are two proposed treatment alternatives. As far as airway stenting is concerned, US Food and Drug Administration does not recommend metal stents if other alternatives are available (tracheal surgery or silicone stenting) (6). Silicone stents were shown to improve functional status and dyspnea immediately after intervention, but are associated with a high rate of complications including mucus plugs, migrations, and granulation tissues requiring repeat bronchoscopies (7,8). Because of the long-term issues with indwelling airway stents, in some centers silicone stents are used only as a bridge to membranous tracheoplasty (in order to assess improvement in symptoms once airway patency is restored by the stent) or as a definitive therapy in non-operative candidates (8).

Open or thoracoscopic surgical techniques are proposed options for patients with severe airway collapse due to TM that also have severe functional impairment (i.e., hospitalizations for pneumonia due to inability to raise
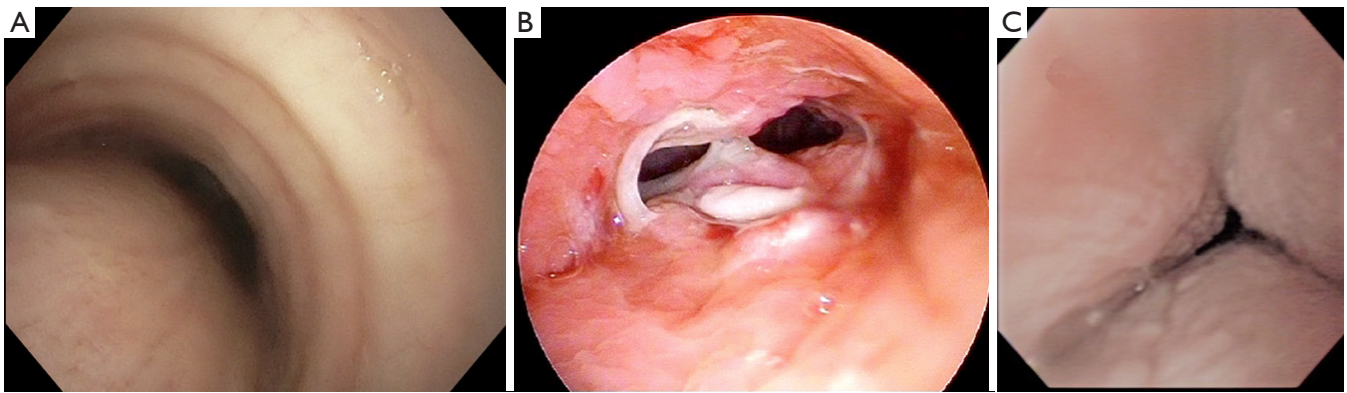
Figure 1 Three distinct forms of ECAC. (A) EDAC with posterior membrane bulging inwards in a patient with severe obesity; (B) crescent-type tracheomalacia with airway edema; (C) circumferential tracheomalacia in a patient with Relapsing Polychondritis. ECAC, expiratory central airway collapse; EDAC, excessive dynamic airway collapse.

secretions or hypercarbic failure). They offer the advantage of being a permanent solution without the need for an airway foreign object (i.e., airway stent). There are several established techniques including tracheobronchopexy, aortopexy, and external stabilization.

Direct tracheobronchopexy could be performed via thoracoscopy or thoracotomy for pediatric malacia and is achieved with either anterior suspension and/or posterior fixation (9). For posterior fixation, sutures are passed through the posterior membrane and secured to anterior spinal ligament. For anterior suspension, the airway wall is elevated by passing sutures through a tracheal ring and then secured to the sternum.

Aortopexy is an alternate surgical treatment for severe TM, which can also be performed either open or thoracoscopically. This procedure involves suturing the aorta to the sternum; the anterior tracheal wall is attached to posterior aortic wall via pre-tracheal fascia and therefore the tracheal lumen is opened. Outcomes with this procedure are variable. In a review of 40 articles reporting on patients who underwent aortopexy for pediatric TM, more than 80% of the patients improved, 8% showed no improvement, 4% had a worsening of their symptoms and 6% died. Complications were observed in 15% of patients and included pneumothorax, pleural effusion, atelectasis, pericardial effusion, phrenic nerve palsy, and bleeding (10).

It remains unclear whether bronchoscopic or open surgical techniques are better for patients suffering from TM although the efficacy and clinical outcomes of aortopexy versus tracheal stents were compared in pediatric patients (11). The authors concluded that both modalities

were effective in the management of TM. However, although aortopexy was associated with early perioperative complications, tracheal stents were associated with higher failure rate and more severe morbidity and mortality. This study generates a hypothesis that open surgery may be preferable for long-term and more sustained response for this disease process.

External stabilization offers a potential solution. One of the first approaches used a Marlex mesh splint reinforced with silastic rings which was sutured in place for a permanent tracheal splinting in pediatric patients with TBM (12). Tracheoplasty (aka tracheobronchoplasty) is a surgical procedure for diffuse TBM in which the membranous portion of the trachea is splinted from the thoracic inlet to the distal left mainstem bronchus and distal bronchus intermedius. It is performed via a right thoracotomy allowing the posterior airway to be exposed after the azygos vein is ligated. The posterior wall of the trachea is reefed to a sheet of acellular dermis (or polypropylene mesh) with a series of stitches from the thoracic inlet to the bottom of the trachea to restore the normal D-shaped airway morphology (13,14). This procedure was shown to improve respiratory symptoms, health-related QOL, and functional status in selected patients with severe symptomatic TBM (15). In one study of 63 patients, however, complications were not uncommon and included a new respiratory infection in 14 patients, pulmonary embolism in two, and atrial fibrillation in six; an additional six patients required reintubation, and nine received a postoperative tracheotomy; 47 patients required postoperative bronchoscopy for aspiration of

secretions. Two patients (3.2%) died postoperatively- one due to worsening usual interstitial pneumonia and the other of massive pulmonary embolism (16). Because of the morbidity and mortality described in previous attempts for external stabilization for TM, searching for safer alternatives is warranted.

In these regards, the surgical technique published by Huang *et al*. in this month's article is the first documented attempt for an external fixation using a personalized scaffold in an adult patient with TM. Previous reports address the use of external tracheal stabilization techniques in animals, but limitations included the restricted growth of the trachea due to the fixed-size implant and the premature splint degradation (17). Three-dimensional printing (3DP) has been used in various medical devices in the past, including many cases of pediatric TM, but has never been reported in adults (18-20). In their case report published in this issue, the authors developed a 270° open-ring scaffold that is bio-absorbable and meant to last for 24 months to maintain the native airway. It is composed of polycaprolactone, which over the 24 months degrades into H_2O and CO_2, causing fibrosis and hyperplasia of surrounding tissues allowing the malacic trachea to solidify. The scaffold was printed after the tracheal malacic segment was recreated using the patient's personal chest CT and bronchoscopy findings. The scaffold was inserted by a posterolateral thoracotomy and required the ligature of the azygos vein and bronchoscopy to choose optimal sites for suture placement. A pleural patch was placed around the 3DP scaffold to alleviate abrasion to surrounding organs. The patient was kept on a ventilator for 48 hours and discharged after two weeks. Follow-up after three months showed improvement in breathing, stable position of the scaffold and maintained tracheal patency on chest CT.

This case report demonstrates a personalized therapy for TM, with the added benefit of not leaving a permanent foreign body within the patient (i.e., airway stent). However, further investigations are warranted with similar techniques in more patients. Long-term follow-up will be necessary to evaluate complications, as well objective documentation of change in symptoms according to validated dyspnea, performance status or QOL scales. Also, to our knowledge, there are no published reports on 3DP biodegradable airway stents that could be inserted bronchoscopically for TM. If feasible, this procedure will preclude the need for thoracotomy and its associated morbidity. Thus, the use of personalized 3DP for TM remains to be defined. Potential therapies recently studied in animal models might include

tissue-engineering techniques with collagenous connective tissue membranes (bio sheets) as a potential tracheal substitute material (21,22). These will have to be validated in humans prior to implementation in practice.

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Tracheobronchomalacia treatment: how far have we come?

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Comment on: Huang L, Wang L, He J, *et al.* Tracheal suspension by using 3-dimensional printed personalized scaffold in a patient with tracheomalacia. J Thorac Dis 2016;8:3323-8.

Tracheobronchomalacia (TBM) is a rather underdiagnosed endobronchial disease which treatment depends on the severity of symptoms as a consequence of severe dynamical tracheal occlusion. To this date there is no consensus regarding the therapeutic approach, hence, new state-of-the-art techniques should be taken into consideration.

Definitions

The spectrum of central airway expiratory dynamic obstruction includes TBM and excessive or hyperdynamic airway collapse. Certain degree of an airway compression characterized by an invagination of the posterior membrane and narrowing of the airway cross sectional area represents a normal physiologic process. When this process is exaggerated due to airway diseases, obesity or even in healthy individuals, the proposed term is excessive dynamic airway collapse (EDAC) (1). TBM signifies diffuse or segmental weakness of the trachea and/or main bronchi (2). While the reduction of longitudinal smooth muscle fibers tightening to prevent excessive expiratory collapse seems to be the reason for EDAC, the loss of cartilaginous structures is the main finding in TBM (3).

Epidemiology

There is scarce evidence on the prevalence of TBM or EDAC and studies in general populations are still required. For example, the incidence of TBM and HDAC was found to range from 4% to 23% in patients with various respiratory symptoms undergoing bronchoscopy (2). One of

the major reasons why this prevalence varies from one study to the other is that the symptoms are commonly mistaken and attributed to other airway diseases such as asthma or chronic obstructive pulmonary disease, and accurate diagnosis could be delayed for years (3).

Etiology

In general, TBM and EDCA can be congenital or acquired. In adults, they are usually acquired or secondary to various conditions divided in airway inflammation (irritant inhalation/aspiration, recurrent airway infections, airway diseases, collagen vascular diseases, prolonged intubation, tracheostomy) or mechanical causes (airway injury or manipulation, chronic external compression) (2-6). Speaking of airway infections, pulmonary tuberculosis may affect any part of the tracheobronchial tree and its incidence has been reported to range from 6% to 50% of cases (7). Stenosis as well as malacia has been previously described, though the clinical conditions underlying tuberculous airway stenosis often involve both cicatricial stenosis and malacia (8).

Classification

A myriad of systems based on features such as location, distribution or severity have been proposed. Although these classifications are purely academic and so far have not demonstrated to be useful in terms of guiding a specific therapeutic attitude, the most recent and increasingly applied classification aims to integrate all these conditions including functional status (World Health Organization 1–4);

extent (normal, focal, multifocal, and diffuse); morphology (EDAC and TBM crescent, saber sheath, and circumferential); cause (idiopathic or secondary); severity [normal (0–50%), mild (50–75%), moderate (75–100%), severe (100%) complete collapse] (9).

Symptoms

Due to the wide range of characteristics taking place in TBM and EDAC, the symptoms may differ from being the patient completely asymptomatic to major signs and symptoms including dyspnea, intractable cough (often barking), recurrent pulmonary infections (e.g., bronchitis, pneumonias) and difficulty expectorating sputum due to impaired mucociliary clearance, wheezing/stridor, hemoptysis and syncope due to cough (2). As stated, there are no specific symptoms orientating to TBM or EDCA, though clinical suspicion and awareness are paramount to detect them.

Diagnosis

TBM and EDAC are diagnosed by means of paired inspiratory-dynamic expiratory chest computed tomography or dynamic (aka functional) bronchoscopy (10-13). These methods are complementary and have high inter and intraobserver agreement. It is important to not over-diagnose these airway complications, although distinguishing them as a primary cause or incidental finding associated with dyspnea is often difficult (14).

Treatment

Treatment of the underlying disease is fundamental to prevent TBM and EDCA progression. However, in cases of severe malacia more active measures are needed.

Positive airway pressure

Considering the intraluminal pressure achieved, increasing positive airway pressure [either continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV)] may overcome the dynamic expiratory obstruction in patients with severe TBM or EDCA as a pneumatic stent, and improve both quality of life and pulmonary function tests. The use of CPAP for TBM was first described in the early 80's and showed that addition of intermittent positive pressure to routine medical therapy

may be of benefit to patients with severe TBM unresponsive to conventional medical management (15,16). NIPPV can be offered with nocturnal and intermittent application during the day, with pressure settings determined during bronchoscopic titration (17). Nowadays, in cases of refractory TBM it is considered as a temporary treatment before surgery.

Stenting

It has been stated that the preferred treatment once a severe TBM has taken place, is airway stenting (14). Although, other groups, based on the current understanding of airflow physiology, recommend that stent insertion should be reserved for patients with severe TBM not responding to the treatment of the underlying disorder and positive airway pressure (1). Similar to CPAP or NIPPV, it is considered a transient measure before surgery or definitive for patients who are not surgical candidates. There is no consensus addressing which type of stent should be used for TBM. However, so far the evidence is in favor of silicone stents rather that self-expandable metallic ones (1,2) in spite of their considerable number of complications, where infections, obstructions due to mucus plugs, migrations, and formation of granulation tissue have been described (18,19). On the other hand, expandable metallic stents are associated with numerous potential problems once inserted. Furthermore, once deployed in the airway they are difficult, if not impossible, to remove. Therefore, their usefulness in the management of patients with benign large airway disease should be carefully questioned (20).

Surgery

Patients with diffuse TBM are selected for surgical treatment if the severity of malacia exceeds that of small airway disease. As stated before, temporary tracheal stenting may help to assess benefits in individual patients, but is discouraged as long-term therapy because of the complications of endotracheal stenting. One of the surgical therapies is membranous tracheoplasty restoring the convex cartilage horseshoe shape by reefing and supporting the membranous wall with a polypropylene mesh (5). In cases of severe localized TBM, resection of the malacic segment with end-to-end anastomosis should be considered. Finally, aortopexy, a surgical procedure that consists in lifting anteriorly the aorta and suturing it to the posterior surface of the sternum has been performed especially in children

with congenital abnormalities (21), but no evidence of its suitability has been determined in adults.

New techniques

Options to surpass the complications in the follow-up period are being developed, especially for airway stenting. Yet there is no sufficient evidence to support the use of these new devices such as biodegradable or drug-eluting stents, it seems feasible in humans giving the case series reported (22). Also, bioprinting technology with 3-D prosthetics has drawn more and more attention as a fabrication methodology for producing scaffolds, cells, tissues and organs, having the advantage of precise control, repeatability and individual design (23).

Conclusions

TBM treatment can be cumbersome and no generalities shall be applied considering the multiple circumstances participating in the disease progression, other that treating the underlying condition. That is why every case should be individualized so physicians, concurring with their patients, chose the best option available. New state-of-the-art techniques are being developed with promising results, for instance 3-D bioprinting, although we still have a road ahead of us in terms of determining their true utility for this complex airway affection.

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Footnote

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An engineering perspective on 3D printed personalized scaffolds for tracheal suspension technique

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Comment on: Huang L, Wang L, He J, *et al*. Tracheal suspension by using 3-dimensional printed personalized scaffold in a patient with tracheomalacia. J Thorac Dis 2016;8:3323-8.

Abstract: 3D printing is a large family of many distinct technologies covering a wide range of topics. From an engineering point of view, there should be considerations for selection of design, material, and process when using 3D printing for surgical technique innovation such as personalized scaffolds. Moreover, cost should also be considered if there are equally effective alternatives to the innovation. Furthermore, engineering considerations and options should be clearly communicated and readily available to surgeons for advancement in future.

Keywords: 3D printing; additive manufacturing; 4D printing; tissue engineering; trachea

3D printing (formally known as additive manufacturing) is a group of technologies that rely on the interaction of mass and energy to manufacture a complex 3D object layer by layer (1). Compared to conventional subtractive and formative manufacturing processes, 3D printing is most suitable for making products characteristic with high complexity, high value, high customization but low volume (as low as one piece). In the medical setting, 3D printings are mostly used for making surgical guides, anatomical models and custom implants (2). 3D printing has also been extensively used in tissue engineering and regenerative medicine as an enabling tool to fabricate customized biodegradable scaffolds with controlled architecture (3-8).

Recently, a 3D printed polycaprolactone (PCL) scaffold is used unconventionally as a new surgical technique to treat a malfunctioned segment of trachea (9). In this study, instead of inserting a luminal stent to expand the collapsed trachea from the internal, the authors implanted 3D printed C-shaped tubular scaffold around the collapsed segment to suspend it from the external. The collapsed segment is attached to the scaffold by using 4–0 Polyglactin (Ethicon, Somerville, USA) sutures. An artificial pleural patch was wrapped around the scaffold to alleviate abrasion to other organs. The patient was discharged from the hospital in 2 weeks after the surgery. In the follow up of first 3 months, the patient had a remarkable improvement in breathing and physical strength, and the cavity of the suspended trachea remained the same.

This is not the first study on tracheal suspension in human, but this is the first report on using a 3D-extruded PCL scaffold in an adult patient (a 46-year-old female). Previously reported cases are limited to the use of laser-sintered PCL scaffolds in paediatric patients (10,11). In 3D printing, 3D extrusion is formally known Fused Deposition Modelling (FDM), which is simple, versatile and cheap compared to laser sintering process. Other medical material such as PEEK can also be printed by FDM (12). Therefore, this study provides complementary information to prior studies at least with regard to the variety of 3D printing techniques. In fact, there are over 50 different commercial 3D printing systems available in the market (1). Their potentials for medical applications have not been fully unveiled.

This study is interesting though, from an engineering

point of view, there are still a few unanswered questions. Firstly, the collapsed trachea is suspended to the scaffold by using bioresorbable sutures without any other fasteners. The bioresorbable sutures are likely to degrade and loosen over one month. However, the follow up study shows that the suspended trachea remained widely open and did not detach from the scaffold or re-collapse anywhere. It is worth finding out what are the forces that suspend the collapsed trachea to the scaffold even after the sutures have degraded. This observation has not been clearly explained in detail.

If it is because the tracheal tissue penetrates into the pores of PCL scaffold and integrates with PCL material, it would signify the importance of scaffold design, in particular the pores. However, it is not clear in this study why a series of solid C rings were chosen for the scaffold design, especially when alternative designs could also be 3D printed, such as a porous tubular structure (13). Although it is difficult to predict which design will lead to the best outcome, at least there is more than one design option for tracheal suspension technique.

Secondly, it is not clear what would the fate of the treated trachea be after the PCL scaffold has completely degraded. If the trachea still remains adequately open, PCL must be involved in the healing or regeneration of the malfunctioned trachea. Then the mechanism responsible for it becomes interesting.

If the treated trachea is at the risk of an ultimate re-collapse after PCL degradation, then why not using 3D printed biocompatible metals (e.g., titanium alloy) with a lightweight design at the beginning? Selective laser melting (SLM) and electron beam melting (EBM) are two established 3D printing methods for fabricating complex lightweight titanium alloys (14). Unfortunately, follow up data more than the degradation time of PCL are not available. It remains elusive whether biodegradable polymeric scaffolds are better than biocompatible metals. Considering that there is also 3D printed biocompatible but non-degradable polymer (e.g., PEEK), the materials suitable for tracheal suspension technique should never be limited to PCL.

In fact, in the case of paediatric patients, PCL is used as a 4D printed material rather than 3D printed material. 4D printing refers to the shape change of a 3D printed material over time when given some stimulus (15). PCL degrades over time and the strength decays, which allows accommodating the growth of a child. Therefore PCL may be more suitable for pediatric patients. However, in an adult patient, it is debatable if PCL is still the best option.

Nonetheless, PCL is a tested and perhaps a safer option in tracheal suspension so far.

Thirdly, 3D printed medical devices have advantages such as personalization and speed, but the advantage on cost effectiveness is not conclusive yet (2). In this study, whether there is any cost advantage for using the 3D printed PCL scaffold over conventional methods is not revealed. However, since the 3D printing technique used in this study is FDM, which is less expensive compared to SLS in previous studies, the increased cost may be balanced by the advantages.

In conclusion, 3D printing is gaining more and more acceptance in surgical practices, including innovation of new surgical technique. If more engineering considerations and options can be clearly communicated and readily available to doctors and surgeons, more interesting advances in this direction should be seen in future.

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Footnote

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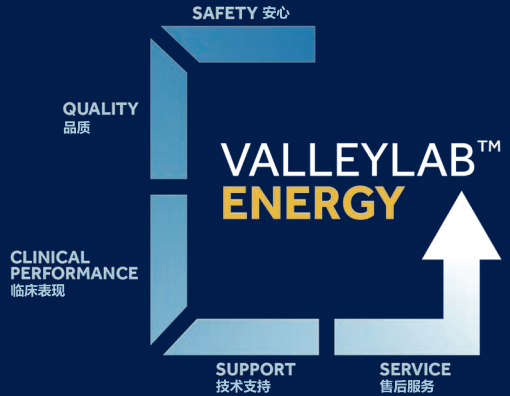
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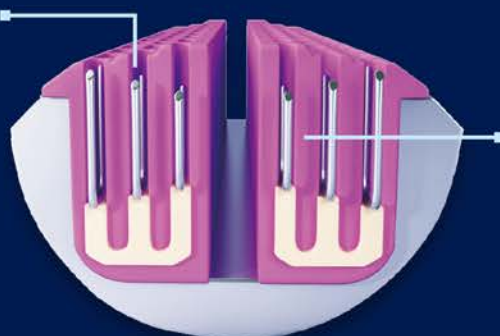速利

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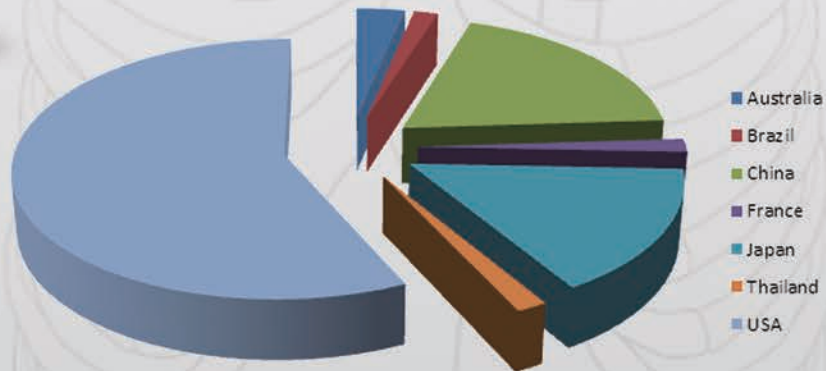
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